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TEXT-BOOK OF PATHOLOGY

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PREFACE TO THE FIFTH EDITION

In preparing this edition I have endeavoured to incorporate the chief advances which have been made in the various branches of Pathology during the five years since the previous edition was published. I have proceeded in the belief that an understanding of principles and an analysis of the chief pathological processes and diseases are of more importance for the student than the acquisition of knowledge about rarer abnormalities. The additions made, which are considerable, are thus chiefly in connection with subjects already treated, though some new subjects have been added. The growth of Pathology, however, has demanded not only additions but also alteration in statement and in mode of presentation. A certain amount of remodelling has been found necessary and some portions have been rewritten. Considerable condensation of description has been found possible in parts of the work and this has afforded space for the new matter without increase in the length of the book. Some re-arrangement has been carried out but this is an alteration of minor importance.

As in the case of former editions, it is a pleasure to me to acknowledge the assistance which I have received in the work of revision. I am much indebted to my former colleagues, Professor Browning, Professor Shaw Dunn, Professor Blacklock and Professor Cappell, for valuable criticism and advice in connection with parts of the book, and to Dr. Janet Niven for help in correcting the proofs. A number of new illustrations have been added and for most of these I am indebted to various friends, as mentioned in the text. To all who have thus rendered me helpful service I desire to offer my warmest thanks. The new photomicrographs, with few exceptions, have been made by Mr. John Kirkpatrick, and I wish to thank him also for the quality of his work.

August, 1941.

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PREFACE TO THE FIRST EDITION

This book is intended primarily as a text-book for students of medicine. It is based on the course of instruction which I have given in Glasgow University, and various expansions and additions have been made, with a view to rendering it more generally useful. The subject of Pathology has now become so extensive that in a book of this size selection of subjects is essential for any satisfactory treatment, and in considering their relative importance I have been guided by two main considerations. I have endeavoured, in the first place, to give due weight to the scientific aspect of the general pathological processes, and, in the second, to describe those pathological changes in the various organs, which are of special importance in relation to Clinical Medicine and Surgery. The subject-matter thus falls into two main portions corresponding roughly with General and Special Pathology, though these terms are not used, as it seems inadvisable, in a book of this nature, to draw any sharp distinction. I have been guided mainly by my experience as a teacher and as a hospital pathologist in carrying out the selection referred to. While the work deals chiefly with the structural changes in disease, I have made it my object also to show the bearing of these on disturbances of function, as studied by the clinician, and to incorporate the principal results of experimental and chemical research.

In conformity with the usual practice nowadays, Systematic Bacteriology has been omitted, as have also the subjects of Diseases of the Special Senses and of the Skin, Tropical Diseases, Parasitology, and Teratology, as these can be satisfactorily treated only by specialists in separate works. I have given for convenience, however, an account of the more important parasites in connection with the lesions produced by them, and of the chief congenital abnormalities in relation to the several organs. I have relied as far as possible on my own observations, but I am, of course, greatly indebted to the works of others. These are too numerous to mention in full, but I should wish to state my obligation to the works on Pathological Anatomy by Aschoff and by Kaufmann, for details in connection with the less common lesions. I have given in footnotes references to other books which have been of value and which are recommended to the student.

It is a great pleasure to me to record my indebtedness to those who have helped me in the work. To my sister, Miss S. C. Muir, who has corrected the proofs, and to my colleague, Professor C. H. Browning, who has read the manuscript and given me valuable criticism, I offer my sincere thanks ; likewise to Professors J. Shaw Dunn and G. Haswell Wilson for several photomicrographs ; to Professor R. Stockman for illustrations from his work, *Rheumatism and Arthritis* ; to Drs. John Cowan and W. T. Ritchie for illustrations from their book, *Diseases of the Heart* ; to Dr. A. H. Drew, Professors A. M. Kennedy, J. H. Teacher, and M. J. Stewart for photographs or blocks ; to Professor E. H. Kettle, Drs. A. Ninian Bruce, J. W. S. Blacklock, D. F. Cappell, E. M. Dunlop, G. W. St. C. Ramsay, and Douglas S. Stevenson, for the loan of microscopic preparations. To all these I offer my grateful acknowledgments. The sources of the figures referred to are indicated in the text. Unless where otherwise stated, the drawings are by Mr. Richard Muir of the Pathological Department, University of Edinburgh, and the photographs of naked-eye specimens and the photomicrographs are by Mr. John Kirkpatrick of the Pathological Department, University of Glasgow, who has assisted me also in the preparation of the Index. In thanking them also, I desire to express my appreciation of the skill and care which they have given to the work. Most of the photographs of specimens are from preparations in the Museum of the Western Infirmary, Glasgow.

R. M.

Glasgow,
August, 1924.

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TEXT-BOOK OF PATHOLOGY

INTRODUCTION

Pathology is the science of disease, or the study of disease by scientific methods. Its scope is wider still, however, as it deals with anything abnormal, and abnormalities in structure may not be attended by disease in the ordinary meaning of the term. The methods of study are those of physiology, and are thus of various kinds—physical, chemical, and anatomical; and they are applied both in observation and in experiment. Disease is manifested, on the one hand, by subjective symptoms resulting from disturbance of function, and, on the other, by objective signs and changes which can be scientifically investigated. Just as in health the different functions depend on and are subserved by structure, so also when function is disturbed, there must be some underlying change in the tissues or organs at the same time. The change or abnormality is ordinarily described as being either morphological or chemical in type. One important department of pathology thus comes to be a search for and study of abnormalities in structure, which underlie and are the causes of symptoms and disturbances of function. Such changes may be of a gross kind and visible to the naked eye, or they may be detectable only by the microscope. We have thus the two departments of study, *pathological anatomy* and *pathological histology*. Again, it may not be possible to find any visible alteration, or *lesion* as it is usually called. For example, in that common disturbance known as fever, there is abnormal metabolism, notably of proteins, as is shown by alterations in excretion and in other ways, but frequently we cannot point to a visible change in the tissues which indicates that this has occurred. So also many rapidly active poisons may cause death, without producing a discoverable lesion which will explain the fatal result. Accordingly, whilst the presence of a structural change as a cause of disturbed function is taken as a working principle, there are cases in which the lesion is too minute to be discoverable as yet; and, after all, alterations visible only under the highest powers of the microscope are relatively gross in nature. From the practical point of view it is important to distinguish between lesions which are capable of resolution or cure so that the part returns to normal, and those which are permanent to a greater or less degree. In an acute catarrh, for instance, complete recovery may take place, whereas, if there are repeated attacks or if the condition becomes chronic, then changes of a permanent character often follow.

Chemical changes in the tissues and fluids of the body in disease, which may be regarded as the expression of disturbances of the functional activities of cells, are of high importance, and our means of investigating them are being steadily improved. Many such changes can be detected by ordinary qualitative or quantitative methods, whilst for others the combination of chemical test with subsequent microscopic examination is necessary—the *microchemical* method. It is, however, essential to recognise that many of the most important changes in the body are inaccessible to ordinary chemical methods. It is known, for instance, that in infection most of the symptoms and tissue changes are due to toxins formed by micro-organisms, but there is no chemical means of detecting these poisonous substances. Their presence and mode of action are discoverable only by indirect or by biological reactions, which will be afterwards described. A similar statement applies to certain substances known generally as antibodies, which appear in the blood in association with the development of immunity, and which are of so much importance in connection with the diagnosis and treatment of disease.

The pathologist, however, has to study not only particular changes in the tissues and organs in any condition of disease, but has to elucidate the methods by which they have been brought about. As was established first by the work of Virchow, all disturbances of function and structure in disease depend upon alteration of the life of cells, evidenced partly by damage and partly by increased activity. There is no such thing as new formation of cells in a structureless matrix, as was at one time believed ; all cells are formed by the proliferation of pre-existing cells—*omnis cellula e cellula.* In this way Virchow placed pathology on a scientific basis as *cellular pathology*, and showed that the basis of the phenomena of any one disease was a series of changes occurring in the cells of the body. The body, however, is something more than a collection of cells with certain properties and potentialities ; it is a co-ordinated whole, and each part is related to the organism as unit. This is, of course, evident in the growth and development of the body, that is, in healthy life ; and equally so in conditions of disease. It is seen not only in the interdependence of structurally related parts, but in the mutual control of different organs.

In the study of the changes in the body in a particular disease, the explanation required will be found to be mainly of twofold nature. (*a*) On the one hand we have to discover a lesion and trace its evolution. Each particular change found represents a stage in a series of changes, and the nature and sequence of these have to be elucidated. For example, the appearance of an acutely inflamed tissue forms a complex picture, and we have to study each individual phenomenon and show how the departure from the normal has been reached. We have thus to deal with certain *pathological processes*, as they are called, and these are for the most part of a general character, and present the same main features wherever they are found. (*b*) On the other hand, we have to discover the *cause* which has started the particular pathological process and has led to the departure from the normal. As we have indicated, Virchow and his co-workers established the importance of structural change in relation to functional disturbance, and showed the nature of the pathological processes concerned. But for a considerable time no explanation of their mode of origin could be given. Such a process as inflammation could be minutely studied and its whole course traced, but nothing could be said of its etiology except in a very general way. It was only when bacteria were shown to be the causes of most inflammatory changes and of many specific fevers, that the idea of morbid entities and the like could be given up and the causation of disease became intelligible. The start, course and termination of inflammatory processes were seen to depend on the vital activity of bacteria, and the problem as to the course of the pathological change came to be one as to the conditions regulating the life and death of bacteria in the tissues. Structural pathology thus had many of its problems elucidated by bacteriology. At a later stage ultra-microscopic viruses were found to behave in a similar way to bacteria and to produce like effects. We shall now say something more in detail with regard to pathological processes and their etiology.

Pathological Processes. When the cells of the body are placed under abnormal conditions or are injured, we see a series of changes taking place ; in other words, a pathological process is started. We shall have to enquire whether such processes are new or peculiar to disease, or whether they merely represent physiological processes in abnormal conditions. As a matter of fact, the latter is the case in the great majority of instances. The changes following injury or damage are always of two essentially distinct types :—

(A) In the first place, there is the direct result of the injury—the extreme degree is the death of the cells, but all degrees of degeneration, short of actual death, are met with. This simply means that living cells are necessarily vulnerable, and some of the changes which follow are the direct effect of the damage done. Such changes are sometimes called *retrogressive*, and they indicate merely that the conditions for healthy cell life have been disturbed.

(B) In the second place, when damage has been done or the conditions are abnormal, a series of *reactive* processes come into play. They have for their object the getting rid of the irritant or abnormal state, and the repair of the damage. The reactions are thus *defensive* and *reparative* in nature and they are of two main kinds, viz. (*a*) increased functional activity and (*b*) increased formative activity. These correspond to processes seen in normal conditions. Increased functional activity, katabolism followed by anabolism, is exemplified by increased muscular contraction, increased secretion, increased leucocytic activity, etc. For example, emigration of leucocytes in inflammation, and their action after emigrating, are not new phenomena ; they are represented by the normal activities of leucocytes on a mucous membrane exposed to bacterial action. Increased formative activity occurs in a variety of conditions to be afterwards described, but a typical example is seen in the process of repair. The cells in relation to the injury actively divide and afterwards form matrix, and they will continue to do so until the breach is filled. This is an example of the lighting up again of a process seen in the growth and development of the organism, and proceeds on similar lines. It is therefore not a new process. Functional and formative activities are usually present in an inverse proportion to one another at a given time, but when the former is in undue amount, involving excessive katabolism, enlargement or hypertrophy of the tissue often follows. Such hypertrophy is seen especially in muscular and glandular tissues, and is compensatory or adaptive in nature. A hypertrophied heart is an abnormal heart, but the hypertrophy itself is not an abnormal process ; it is the particular condition which brings it about that is abnormal. As regards its nature, it is analogous to the hypertrophy of the uterus which occurs in pregnancy. Accordingly, in all these reactive changes we see nothing peculiar to disease—the processes observed correspond with those met with in the normal development and life of the individual.

There is, however, one phenomenon of disease which cannot be explained on these lines, namely tumour growth. Here we have to deal with a proliferative process which, so far as is known, is not of a reactive nature—an indefinite and independent proliferation of cells, to which there is nothing analogous in the life of healthy organisms.

To summarise : In pathology we have to investigate by scientific methods the basis of disease—the changes underlying its symptoms, and its functional disturbances. Some of these changes can be seen, others can be detected by chemical or biological reactions, whilst in other cases no important changes have yet been demonstrated. The various changes met with represent in part the result of damage, and in part are of a reactive nature ; they are to a large extent defensive and reparative.

Etiology of Disease. In searching for causes of disease, we go on the general principle that a healthy organism will remain healthy unless it is affected by some disturbing cause from outside. Disease does not occur spontaneously, as no change occurs without a cause. Of some phenomena, however, no explanation can be given ; for example, the cycle of events in the life history of the organism, noticeably the occurrence of senescence. In the great majority of cases the disease or abnormal state is due to some disturbance acting after birth, that is, it is *acquired*. In a relatively small proportion of instances it is present at the time of birth and is then spoken of as *congenital*; but in this type the abnormality may arise during foetal life in various ways, and sometimes in the same manner as in the acquired form. Causes of disease are sometimes spoken of as external and internal, but the terms are inadvisable, as nothing is really known regarding internal causes in the strict sense—that is, the causes of inherent defects or abnormalities of cells or their arrangement. We may say that every *known* disturbance is external or comes from without so far as the affected cells are concerned.

It is unnecessary to discuss the nature of causality, but certain points bearing on the etiology of disease may be referred to. Strictly speaking, we may say that in any physical phenomenon the cause is energy which becomes transformed; for example, in the steam engine the energy of heat becomes transformed into the energy of motion and is thus the cause of motion. But unless the engine is started it does not work and the energy required for starting may be very small; in physics we may thus speak of releasing causes. In biological phenomena the matter is more complicated still and a number of circumstances may be necessary to bring about a given result. We speak of the tubercle bacillus as the cause of tuberculosis in the sense that the introduction of the bacillus is ordinarily followed by the disease and that the latter is not met with apart from the bacillus. But in any one case of tuberculosis several contributory factors may be necessary in order to allow the action of the bacillus to become effective. There must be the necessary susceptibility, and this may be congenital or acquired. Accordingly, with regard to many conditions we have to speak of predisposing, contributing or auxiliary causes. This question of causation will be met with in a more complicated form still when we come to consider the etiology of tumour growth.

We shall merely sketch the chief causes of disease as, at this stage, it would not be of advantage to the student to have them enumerated in detail.

(A) In the first place, reference may be made to abnormal states which are present at birth; these are of various kinds. A few of them are hereditary in the strict sense, depending on abnormalities in the germ plasm, and we assume that such abnormalities are caused in some unknown way by disturbances in the past. Of such truly hereditary conditions, we may mention as examples, colour-blindness, albinism, hæmophilia, some diseases of muscles, etc. Predisposition or susceptibility to certain diseases also is transmitted by heredity, just as are peculiarities in external configuration. Thus, for example, a predisposition to tuberculosis is hereditarily transmitted and experimental research has shown that the same obtains to an extent in tumour growth. In some instances, disease present at birth is the result of intra-uterine infection of the fœtus, the commonest and most striking example of this being congenital syphilis. Lastly, there is the whole group of congenital abnormalities due to errors in development. The cause of these cannot be correctly assigned, but no doubt intra-uterine disturbances—traumatic, nutritive and infective—are largely responsible.

(B) With regard to the causes operating after birth, the following are the main types :—

(1) *Improper or Insufficient Food Supply* : with this may be classed insufficient supply of oxygen. A defect in the amount of food as a whole leads to wasting, and when this is extreme, as in starvation, a condition of inanition is produced which may lead to death. Deficiency in any of the main classes of foodstuffs also brings about harmful results. For example, a variety of œdema occurring on the Continent during the war was found to be mainly the result of protein deficiency in the diet. And of great importance are the 'vitamins' or accessory food principles, the presence of which in sufficient amount is necessary for a state of health. Insufficiency or lack of such substances cause important conditions like scurvy, beri-beri, rickets, etc., which in consequence are regarded as *deficiency diseases*. We thus see that imperfect food supply may be simply of quantitative nature, it may involve lack of one of the main food constituents, or again it may be of more special nature and due to the absence or deficiency of one of the accessory food principles. Furthermore, it may be added that definite pathological effects may be produced by deficiency in various inorganic substances, such as iron, calcium, etc.

(2) *Overwork or Overstrain*. Each organ has a reserve power so that special functional demands may be made without injury. When, however, these demands are excessive, a condition of exhaustion may result, and when this is severe or occurs repeatedly, permanent damage may take place. An organ which is thus impaired may be sufficient for the performance of normal function but may fail when abnormal demands are made on it, and serious results may follow. The effects of exhaustion are seen especially in connection with the circulatory and nervous systems. Further, in the case of the former, the demand for overwork when continued for some time leads to a condition of hypertrophy of the specialised cells, and this may be followed by a failure of the hypertrophic process. In this manner permanent changes of an important kind, both in the heart and in the arteries, may be brought about.

(3) *Trauma or Mechanical Injury*. The effects of trauma need no explanation, but it is important to recognise that, apart from the grosser effects, damage may result in the internal organs from such conditions as concussion. Such damage is of all degrees of severity, and in the case of the central nervous system, important functional disturbances may be produced even when there is little or no discoverable structural lesion.

(4) *Physical Agencies*—Heat, Electricity, etc. Both local and general effects may be produced by extremes of heat and cold. The effect of heat applied locally is the production of burns of varying

degree, extreme damage being an actual charring of the tissues. Exposure to a temperature sufficient to cause coagulation of the cell proteins will of course cause death of the cells ; but at a temperature lower than this, serious damage may be inflicted, and marked inflammatory reaction is a common result. The local action of cold, sometimes resulting in frost-bite, is chiefly on the blood vessels, and leads to a condition in which the circulation can no longer be maintained through a part. Here again, varying degrees of ultimate damage are met with.

As regards general effects, exposure to a hot atmosphere, especially when it is associated with moisture, may lead to pyrexia and other serious results, which are described under the heading of heat-stroke (p. 207). Exposure to cold, resulting in a chill, was formerly regarded as a fruitful cause of various inflammatory conditions. Its importance is considerable, but we now recognise that it acts mainly by leading to vascular disturbances and to a diminished resisting power of the tissues, and thus to invasion by bacteria. Accordingly, the diseases which arise in this way are really of the nature of infections, and the entrance of bacteria will be aided by any other condition of depressed vitality.

Sudden death may of course be caused by *electric currents* of high voltage, and burning or even laceration of the tissues may be present ; on the other hand there may be little change discoverable. Important results of local nature may be caused by certain forms of radiation, notably by X-rays. Such results, which are specially met with after an X-ray ‘ burn ’ and repeated applications, may become distinctly manifest only some time after exposure, and then gradually increase in severity. Corresponding effects are produced by radium.

(5) *Micro-organisms.* Under this term may be included bacteria, protozoa, and various ultra-microscopic viruses or filter-passers. The majority of serious diseases and, in fact, all infective fevers, are produced in this way. The special feature of micro-organisms as a cause of disease, is their power of multiplication in the tissues, and the possibility of their being transferred to other individuals. The action of such organisms in relation to disease will be referred to from time to time, but it is important to recognise that their harmful effects are due to toxic substances which are set free by their action. Infection is thus of the nature of intoxication, and the peculiarity is that there is a progressive manufacture of the poison by the growth of the organisms.

(6) *Other Parasites.* Disease may result from invasion of the tissues of the body also by parasites of higher orders—animal parasites such as cestodes, nematodes, etc. These may be conveniently put in a separate class, as their effects are in certain instances produced in a mechanical way. For example, a hydatid cyst may lead to a fatal result by pressure on important structures. It is to be recognised,

however, that in the case of metazoa also, toxic action is often concerned in the production of harmful effects. Thus, for instance, invasion of the tissues by the *Trichinella spiralis* (p. 852) is attended by fever which may be of considerable intensity and simulate typhoid.

(7) *Chemical Agents, Poisons, etc.* Substances to which the term poisons is applied, are of great variety as regards both their nature and their mode of action. A fundamental distinction is to be drawn between poisons which are introduced into the body as such, and those formed by organisms which have invaded the tissues. The most important difference is that the effects of the former depend on the amount introduced, that is on the dose, whereas with the latter the supply of the poison is regulated by the multiplication of the organisms. The term *toxins* is usually applied to the poisonous products of micro-organisms, though it includes also closely similar poisons of animal and vegetable origin. Poisons introduced into the body from without are usually of known constitution, and the disturbances produced by them may be local or general, and of acute or chronic nature. At one end of the series are the so-called corrosive poisons which have a direct local action, and the effects of which can be explained in most instances by their action on organic material outside the body, such processes as disintegration or coagulation of proteins, etc., being produced. At the other end of the series we have the group of active poisons such as alkaloids, hydrocyanic acid, etc., which act after absorption, and which may be fatal in very minute doses. The study of such poisons belongs to pharmacology and toxicology, but it is to be recognised that in cases of chronic poisoning, structural changes result from their action and have to be investigated by the pathologist. Such changes are well seen in chronic poisoning by alcohol, lead, arsenic, etc. The toxins formed by micro-organisms are apparently of protein nature, but their exact constitution is unknown. Some of these, for example the tetanus, diphtheria, and botulinus toxins, have a characteristic action on certain tissues or organs; but, on the other hand, the effects of the toxins of many bacteria closely resemble each other and are of a general nature, fever with its various accompaniments being a common result. Another peculiarity is that when a bacterial toxin is injected into the body of an animal, there may be a considerable interval or period of incubation before the symptoms and other effects appear; this is well exemplified in the case of diphtheria and tetanus toxins. This delayed or gradual action is seen also in the *local* effects of poisons formed by bacteria. Whilst a chemical irritant acts at once and alike on mucous membranes and on the deeper tissues, bacterial toxins have no such rapid and general action. On the contrary, their action is gradual, often selective, and depends on some subtle interaction with living cells, which cannot as yet be explained on chemical principles. Some bacterial toxins

have the property of giving rise to the formation of antitoxins, as will be described later.

There is no doubt that, in addition to the production of toxins by organisms which have invaded the tissues, there may take place in pathological conditions of the alimentary tract, abnormal fermentative processes followed by the absorption of substances which act as poisons. To this form of poisoning the term *auto-intoxication* has been applied, although it must be recognised that comparatively little of a definite nature is known with regard to it. Substances which act as poisons, or have harmful effects at least, may accumulate in the blood as a result of interference with normal processes of excretion. This is specially exemplified in the case of the kidneys when their excretory functions are interfered with ; it is also a marked feature in obstruction to the outflow of bile.

The above is a mere summary of the main types of causes of disease or abnormal states, and it will be noted that the causes mainly represent conditions of external origin which injure cells or interfere with their normal life. The action of any one of these is up to a point intelligible, and the effects are the production of damage and the setting up of reaction, as explained above. In some instances the primary cause acts locally, in others, on various parts of the body at the same time ; but in the former case the primary lesion may in its turn act as a cause and lead to secondary effects elsewhere. This is especially the case when an organ is injured, and an intimate knowledge of the interaction of the various organs in this respect is of the highest importance both in pathology and in its clinical applications. As a matter of fact, in many instances more is known with regard to this interaction of organs with production of secondary lesions and chemical changes, than with regard to the primary cause. The primary change in many chronic infections includes degeneration of the specialised or functioning cells and an overgrowth of connective tissue, and it indicates a slowly acting cause. But the cause has often been in action for a considerable time before any abnormality is recognised, and hence the elucidation of the etiology is rendered difficult or impossible. This will be abundantly exemplified in the discussion of chronic lesions of the kidneys, liver, nervous system, etc.

We have given an outline of the chief modes in which morbid conditions are brought about, but no reference has been made in it to the very important subject of tumours or new growths. This subject, however, can be discussed with profit only at a later stage.

CHAPTER I

DISTURBANCES OF THE CIRCULATION[1]

In this chapter we shall consider certain disturbances which may affect the circulation generally, or which may occur locally. We shall first speak of abnormalities in the distribution of the blood. These may be of the nature either of excess or of diminution of the blood in any particular area. Excess of blood in a part is called *congestion* or *hyperæmia*, whilst the term *local anæmia* or *ischæmia* is applied to all degrees of diminution, the extreme being complete deprivation of blood. Congestion or hyperæmia may manifestly be produced either by increase of the flow of blood to the part or by interference with the flow from it. The former is due to an active dilatation of the arterioles and is usually called *arterial* or *active hyperæmia*; whilst the latter is the result of venous obstruction and is produced mechanically, and the term *venous* or *passive hyperæmia* is accordingly applied. These are the two main types ordinarily recognised, but in addition, in certain circumstances, there may be excess of blood in a part when neither of these two factors is present and where the accumulation of blood depends either upon an active dilatation of the capillary walls or on some damage to them; in other words, there may be an *independent capillary hyperæmia.* The term active hyperæmia can accordingly no longer be used as synonymous with arterial hyperæmia, since in active hyperæmia an active dilatation of capillaries may also play a part and may even be the chief factor. On the other hand, independent capillary hyperæmia cannot always be regarded as of the active type as it may sometimes represent a state of want of tone. We shall now consider these different forms of hyperæmia.

ARTERIAL HYPERÆMIA

This, as has been said, is produced by a dilatation of the arterioles, and there is thus an increased supply of blood to the particular area. The dilatation leads to diminution in the frictional resistance to the blood flow, and thus there is a rise of pressure in the terminal arterioles, which extends to the capillaries. The latter become widened and the rate of flow through them is increased, whilst they appear to become more numerous, as some which were formerly empty become dilated (Fig. 1). At the same time, there is a slight increase of lymph formation owing to their dilatation and the increased intra-capillary pressure. The pulse wave extends farther down, and may appear in the capillaries or even in the minute veins. Arterial hyperæmia is a physiological process and is to be regarded as the normal response when there is a call for an increased supply of blood. It may be produced by paralysis of the vaso-constrictor nerves or by stimulation of vaso-dilators, directly or reflexly ; and in conditions of disease we find arterial hyperæmia corresponding to these different modes of production. Active hyperæmia results also from the action of chemical substances which act as stimulants, or slight irritants, e.g. mustard, turpentine, and the like ; also from heat in mild degree. And another important point is that temporary anæmia of a part is followed by active hyperæmia when the circulation is restored. This is of importance in connection with bloodless operations, as the full degree of hyperæmia is not established till some time after the circulation has been restored, and thus bleeding may occur from the smaller blood vessels if they have not been ligatured. If, however, the anæmic condition be kept up too long, actual damage may follow and stasis may be the result. Active hyperæmia thus represents a physiological response and is similar to what occurs in connection with increased functional activity ; there is no evidence that there is any damage to the circulatory apparatus. When the part which is the seat of arterial hyperæmia is on the surface of the body, the increased flow of blood through it will produce a rise in its temperature.

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[1] For further details reference may be made to Cohnheim's *Lectures on General Pathology* (New Sydenham Society), London, 1889; and to Thoma's *Text-Book of Pathology* (translated by A. Bruce), London, 1896. Account of recent work on capillaries will be found in *The Anatomy and Physiology of the Capillaries*, by A. Krogh, 2nd edit., London, 1936, and *The Blood Vessels of the Human Skin and their Responses*, by Sir Thomas Lewis, London, 1927.

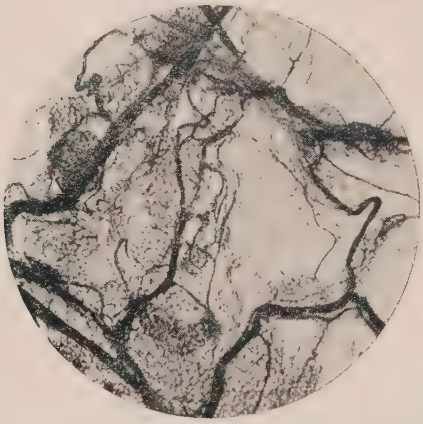

Fig. 1.—Acute Hyperæmia of Omentum showing Engorgement of minute Arteries and Network of distended Capillaries. (Prof. G. Haswell Wilson.) × 20.

CAPILLARY HYPERÆMIA

It may now be regarded as established that the capillaries have independent powers of dilatation and contraction ; in other words, their size and the amount of the blood which they contain do not depend merely on the condition of the associated arterioles. In some cases a nervous reflex is concerned in the changes of their lumen, but chemical and other agencies may act *directly* on their walls. Under normal conditions a considerable proportion of the capillaries are in a collapsed condition and contain no blood, and these empty capillaries may become filled when arterial dilatation takes place. Sometimes, however, considerable dilatation of the arterioles is necessary to open up all the capillaries, and in many cases of active hyperæmia above referred to, the condition of the capillary circulation is, in part at least, the result of an independent dilatation of the capillaries. It has been found by direct observation that a very slight stimulus applied to capillaries may lead to contraction, that a stronger stimulus may cause dilatation, and that the dilatation and congestion may then extend for a considerable distance around. The last result occurs when the corresponding spinal nerve roots are divided but not when the nerves to the part are in a degenerated condition ; accordingly, the dilator effect in the normal state would appear to be partly a direct one on the capillary wall and partly one in which a peripheral reflex is concerned (A. N. Bruce).

These vascular responses are well illustrated in the case of the skin, as has been shown especially by Lewis, whose work has led to results of high importance. Light stroking of the skin is followed by a line of pallor along the stroke, due to active contraction of the capillaries and small vessels—' white reaction ' ; if a greater stimulation is produced by firmer stroking, a band of redness appears—' red reaction.' These two reactions are due (*a*) to contraction, and (*b*) to dilatation of the capillaries respectively ; they are independent of the flow of blood as they occur when the circulation is brought to rest. Still greater stimulation leads to spread of redness to adjacent parts—the ' flare ' ; this may be accompanied in certain cases by whealing, which is a local œdema. The flare is due to reflex dilatation of neighbouring arterioles, and integrity of the cutaneous nerves is necessary for its occurrence. These three phenomena, red reaction, flare and whealing, constitute Lewis's ' triple response ' and have been shown to be due to the release of a diffusible substance from the cells of the skin. This substance has an action closely similar to that of histamine, though the identity has not been conclusively proved. It is called by Lewis the H-substance. Certain individuals are very sensitive to stimulation and whealing of the skin occurs very readily ; if in them much whealing is produced, the symptoms which follow closely resemble those produced by small doses of histamine. Such individuals are not, however, more sensitive to histamine than are normal persons and their peculiarity is due to their tissues setting free the H-substance in abnormal quantity. Other facts with regard to the release of the H-substance are brought forward, but for further details reference must be made to the original work (p. 11). It is clear, however, that Lewis's results have a wide application to the reactions of tissues in general. The relationship of a histamine-like substance to shock is described later, and it would appear that many vascular reactions to injury are really an evidence of the effect of a similar substance acting on a small scale. There is also evidence that in the phenomena of anaphylaxis the setting free of H-substance is concerned; at least certain of the phenomena are such as might be produced in this way (p. 194).

There are conditions where the capillaries are dilated and the arteries contracted. When, for instance, the hands are exposed to cold, congestion is sometimes associated with blueness and coldness of the parts, and in this case, as pointed out by Bayliss, there is an impaired circulation owing to contraction of the arteries, whilst the capillaries are dilated and the blood within them is imperfectly oxygenated, There is neither arterial dilatation nor venous obstruction, and the congestion is apparently the direct effect of cold on the capillary walls. As will be explained more fully below, histamine leads to contraction of the arterioles and dilatation of capillaries, and adrenalin in small doses has a corresponding effect. It must be noted that dilatation of capillaries alone in a particular area, though increasing the amount of the blood in the part, will not be attended by increase in the *rate* of blood flow, unless there is at the same time arterial dilatation; in fact it will act in the other direction. This follows from the fact that the capillary bed is so much wider than the sectional area of the corresponding arterioles. But when arterial dilatation is present, independent capillary dilatation will accentuate the phenomena, and thus will play a part in producing active hyperæmia—for example, that preceding inflammation (p. 61).

Capillary dilatation following various forms of stimuli, mechanical, chemical, thermal, etc., usually occurs almost at once, within a few seconds, but this is not always the case. When, for instance, the skin is exposed to the rays of a Finsen lamp, the capillary dilatation does not occur till some hours afterwards, and then the capillaries may remain in a dilated state for days. This chronic dilatation, as it may be called, is apparently the result of a loss of tone and probably represents the effect of minimum damage. The difference between heat rays and ultra-violet rays in this respect is noteworthy, and a remarkable example of delayed effect is seen also in the case of X-rays. Capillary hyperæmia may thus be transitory or it may last for a time, and in the latter case the capillaries have probably suffered some slight injury which is not soon repaired. As will be described later in connection with inflammation, if the damage be more severe the flow of blood through the capillaries is interfered with and its rate diminished. The extreme degree of this is complete stoppage of the flow or stasis (p. 62). This may be recovered from, the flow being restored; but a still more severe injury to the capillaries may cause necrosis of their walls and thrombosis, and then restoration of the circulation is impossible. These different degrees of capillary injury are often accompanied by altered permeability of the wall, leading to transudation, exudation, etc., and are of great importance in connection with various pathological processes, as will be seen later.

VENOUS CONGESTION OR PASSIVE HYPERÆMIA

Two varieties of this condition are to be recognised, namely *general venous congestion*, in which the whole venous system is affected, and *local venous congestion*, where the excess of blood is present only in a certain area. Although the change is essentially the same in the two cases, the causation and results are somewhat different, and the two varieties are to be described separately.

General Venous Congestion. This condition is of great importance in view of its frequency and the serious results which may follow when it is long-continued. As has already been stated, there is an excess of blood in the venous system throughout the body, and we have to consider how this state is brought about. General venous congestion may occur somewhat rapidly, often a short time before death, and at post-mortem examination all the organs show venous engorgement ; it may also be a temporary condition and may be recovered from. The essential factor in its production is diminished output of blood by the left ventricle, as will be explained below. The important form known as *chronic venous congestion* is of long duration, is usually of a more or less permanent nature, and brings about important structural alterations. The cause of chronic venous congestion is one resident either in the *heart* or in the *lungs*, as these are the organs through which the whole blood passes in each complete circulation. Thus we find that it results from valvular disease of the heart, or from lesions of the cardiac muscle, or from certain diseases of the lungs. The two chief pulmonary diseases which affect the circulation are emphysema and fibrosis. In the former there is a great atrophy of parts of the walls of the air vesicles, and hence the capillary area is diminished, while at the same time many of the surviving capillaries are stretched and therefore narrowed. From both of these causes the flow of blood through the lungs is impeded. In fibrosis also, there is obstruction to the blood flow, as part of the pulmonary tissue is replaced by the less vascular connective tissue, and the latter may also undergo considerable contraction.

If, however, we examine the various conditions which cause general venous congestion, we find that they all have this in common—they lead to a diminution in the amount of blood passed into the aorta in a unit of time. This would lead to a fall in the arterial blood pressure, if there were no compensating mechanism, seeing that the pressure depends on the amount of blood passed into the aorta and on the peripheral resistance. But in the various conditions of diminished output mentioned, it is found that, at least for a considerable time, the blood pressure is maintained about the normal, and this is brought about by a tonic contraction of the arterioles. The amount of blood in the arterial system is thus diminished, while there is an increase in the veins—in other words there is a general venous congestion. Later, however, the blood pressure may fall, the circulation then becomes more embarrassed and the heart ultimately fails.

The accumulation of blood in the venous system may be allowed by passive dilatation of the veins, and theoretically need not involve a rise of the pressure in them ; and various observers have failed to find any such rise. But at certain stages the tendency to further dilatation against the resistance of the vessel wall may bring about an increase in the venous pressure. For example, in cases where there is extreme venous engorgement with cyanosis, and venesection is performed, the blood may spurt from the incised vein, indicating a considerable amount of increased pressure. In general venous congestion the amount of blood passed through the circulation in a unit of time is diminished, while the capillaries contain an excess of blood with a larger proportion of reduced hæmoglobin than the normal; hence the oxygen supply to the tissues may be interfered with and various degrees of anoxæmia and cyanosis result. There tends also to be coldness of the skin surface. The most important general effects which may arise from chronic venous congestion are thus: anoxæmia, cyanosis, œdema and certain structural changes. Œdema will be more conveniently dealt with later (p. 43) ; the other three may now be considered.

Anoxæmia.[1] This term, which really means deficiency of oxygen in the blood, is applied to the various conditions in which the oxygen supply to the tissues is interfered with. This may be due to lowered oxygen saturation of the arterial blood—*anoxic type* (p. 374), or to deficiency in the actual or available hæmoglobin in the blood—*anæmic type* (p. 458). In the present instance the anoxæmia is due to deficiency of oxy-hæmoglobin within the congested capillaries and is spoken of as the *congestive* or *stagnant type*. It may be noted that the oxygen available for the tissues is that dissociated in the plasma, and this depends on the amount of oxy-hæmoglobin in the red corpuscles. As the oxygen in solution is used up by the tissues additional oxygen separates from the oxy-hæmoglobin. In normal arterial blood, for example, the oxygen in solution is about one-fiftieth of the oxygen combined with hæmoglobin (Haldane). It is thus evident that in the passively congested capillaries in which the degree of oxygen saturation of the hæmoglobin is below the normal, the amount of oxygen in solution will also be reduced and thus the supply to the tissues will be diminished. The normal degree of oxygen saturation of arterial blood is about 95 per cent. while that of venous blood is about 65–75 per cent. In the congestive form of anoxæmia the difference between the arterial and venous saturation is greater than the normal of 20–30 per cent., for the reasons stated. It is to be observed, however, that general chronic venous congestion due to cardiac disease may exist without anoxæmia. It is especially when cardiac compensation begins to fail and the cardiac output is still more diminished that the oxygen unsaturation of the venous blood becomes increased. Further, in the later stages of cardiac decompensation with œdema and other changes in the lungs, the aeration of the blood in the pulmonary capillaries is interfered with. Thus the arterial saturation also may fall below the normal ; that is, anoxæmia of the *anoxic* type may be superadded, and then the degree of venous unsaturation becomes increased.

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[1] For further details on this and allied subjects, see *The Chemistry of the Blood in Clinical Medicine*, by O. L. V. de Wesselow, London, 1924.

The existence of long-standing congestive anoxæmia cannot be without effect on the general nutrition. Thus, for example, it leads to fatty changes in the liver and it may be concerned in the production of the œdema which often occurs at a later stage (p. 43).

We may mention also that in cases of congenital heart disease, e.g. pulmonary stenosis with deficiency in the interventricular septum, the anoxæmia has a cause additional to the venous congestion, viz. an admixture of the arterial and the venous currents, part of the blood from the right ventricle passing to the left ventricle and onwards to the aorta without going through the lungs. In such cases the degree of oxygen saturation of the arterial blood will be lowered ; that is, there will be an anoxic anoxæmia in addition to any congestive anoxæmia present.

Cyanosis. We have referred to the occurrence of cyanosis in connection with chronic venous congestion, but it will be convenient to give some additional facts at this stage. The term is to be taken as a descriptive one, indicating varying degrees of blueness or lividity of the skin and mucous membranes, resulting from an increased amount of reduced hæmoglobin in the capillaries and small veins. Cyanosis depends mainly on the amount of reduced hæmoglobin, though the relative transparency of the skin and other tissues also plays a part. Unsaturation of the hæmoglobin alone does not produce it—a certain *amount* of reduced hæmoglobin must be present. For example, in severe anæmias the degree of venous unsaturation may be much higher than in venous congestion and yet cyanosis may not be present.

The chief conditions producing cyanosis may be said to be : (*a*) Accumulation of blood in the capillaries with diminished rate of flow through them. This is seen in chronic venous congestion of marked degree, as has been described. It occurs also when a similar condition of the capillary circulation is produced by exposure to cold (p. 14). Here also the hæmoglobin within the capillaries parts with its oxygen to the tissues and there is an increased amount of reduced hæmoglobin. It may be noted that the initial action of cold is usually a general contraction of arterioles and capillaries, whilst after a time the capillaries become dilated, apparently from loss of tone, and the cyanosis occurs. These two effects of cold are seen in intensified form, in the 'local syncope' and 'local asphyxia' of Raynaud's disease (p. 310). (*b*) Cyanosis may occur also from deficient oxygen saturation of the arterial blood, such as occurs in pulmonary disease with deficient aeration, e.g. in some cases of pneumonia, pulmonary œdema, etc., the oxygen saturation of the venous blood falling in proportion. Further, cyanosis tends to occur from this cause in individuals living at a high altitude, especially when any exertion is made. But in many cases of extreme cyanosis there is a combination of the two factors (*a*) and (*b*). (*c*) Cyanosis is often a prominent feature in cases of congenital heart disease with admixture of the venous and arterial streams—hence it is called 'admixture cyanosis.' This is well seen, for example, in pulmonary stenosis with deficiency in the interventricular septum, as mentioned above. In such cases, too, the percentage of hæmoglobin, owing to polycythæmia, is above normal, and as it is largely in a reduced form within the capillaries the cyanosis is thereby intensified.

General venous congestion may exist for a long time without the occurrence of any *œdema* but after a certain period œdema may appear, at first in the tissue round the ankles, and then steadily increase. The nature of this condition is considered below.

STRUCTURAL CHANGES. When chronic venous congestion has existed for some time, characteristic changes are brought about in the organs. Not only are they somewhat swollen, and of purplish colour owing to excess of venous blood, but they become firmer in consistence, as is seen very well in the case of the kidneys and spleen. Hence the term *cyanotic induration* is applied, and the change appears to be due chiefly to thickening of the capillary walls in response to the state of over-distension; probably there is also some increased density of the interstitial tissue, though there is usually no distinct fibrosis to be found on microscopic examination. In the *lungs*, red corpuscles escape from time to time from the distended capillaries, their hæmoglobin is broken up, and hæmosiderin and other brown pigments are formed; these are taken up by phagocytic cells which may accumulate in the alveoli in considerable numbers (Fig. 2). These cells are often known as 'heart-failure cells,' but the term is misleading as they are met with when there is no heart failure; in fact, all that is necessary for their formation is an escape of red corpuscles into the alveoli, such as may occur in mitral stenosis when the heart's action is satisfactory. The origin of the phagocytic cells is discussed later (p. 169). The pigment is then carried from the alveoli into the tissue spaces of the lungs and becomes distributed through their substance. It may become very abundant, as is readily shown by treating sections with hydrochloric acid and ferrocyanide of potassium. Hence, in addition to being tougher or firmer than normally, the lung tissue has a brownish tint—the condition being known as *brown induration*. In the *liver*, congestion is most marked in the central parts of the lobules, where the liver cells undergo atrophy and ultimately disappear; the central zone is then constituted by the capillaries and stroma (Fig. 3). At the same time there occurs an accumulation of fat round the portal tracts, and thus the lobules become marked out into dark red and yellow areas respectively, the term 'nutmeg liver' being applied, from the mottled appearance (Fig. 4). These atrophic and fatty changes are chiefly the results of anoxæmia. Owing to the change

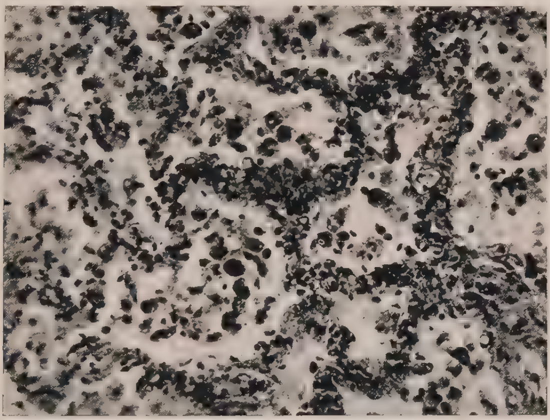

Fig. 2.—Lung in Chronic Venous Congestion, showing Thickening of Alveolar Walls and Varicosity of Capillaries; cells containing blood pigment are lying free in alveoli. (G.H.W.) × 100.

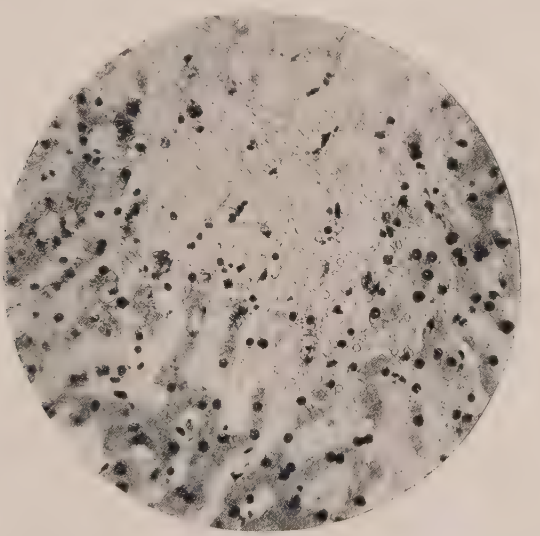

Fig. 3.—Liver in Chronic Venous Congestion, showing Atrophy and Disappearance of Liver Cells; in the upper part of the figure they are replaced by wide capillaries or sinusoids. × 250.

in the central parts of the lobules, there results a considerable loss of liver parenchyma and thus compensatory changes in the form of

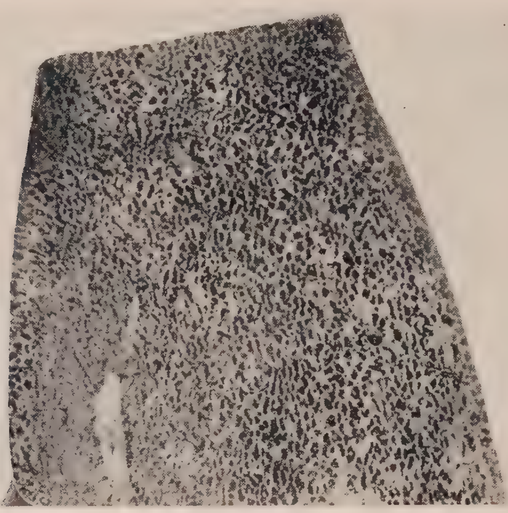

Fig. 4.—Liver in Chronic Venous Congestion—'Nutmeg Liver.'
Note the dark congested central parts of lobules, and pale periphery due to fatty change. (Natural size.)

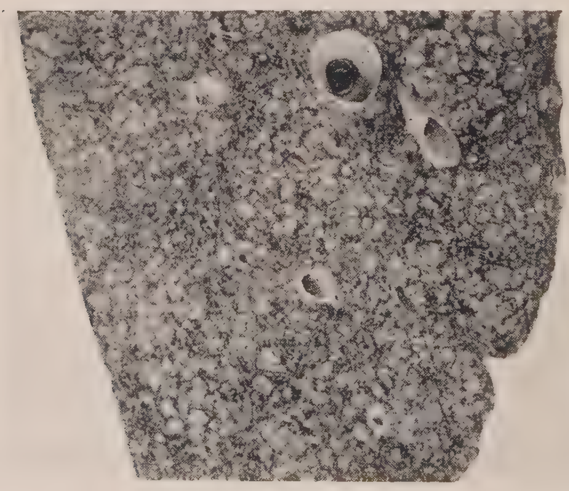

Fig. 5.—Liver in Chronic Venous Congestion, showing numerous small Hypertrophic areas of pale appearance. (Natural size.)

hypertrophy and hyperplasia of surviving liver cells may follow. The hypertrophic areas, which are pale in appearance, may be small and fairly regularly distributed (Fig. 5), or they may be of larger size and irregular in form and distribution. These hypertrophic changes are seen, however, only in long-standing cases and tend to occur especially in young patients.

Local Venous Congestion. This is brought about by mechanical interference with the return of blood from a part—by the formation of a thrombus within a vein, or by pressure from outside, e.g. by a tumour or an aneurysm, by the contraction of fibrous tissue, etc. It may occur rapidly or be slowly produced.

(*a*) If a vein is *rapidly obstructed,* say by a thrombus or by a ligature, there occur in the related area phenomena corresponding to those described above. A certain amount of swelling and lividity is seen, and, if the part is on the surface, also some fall in the temperature.

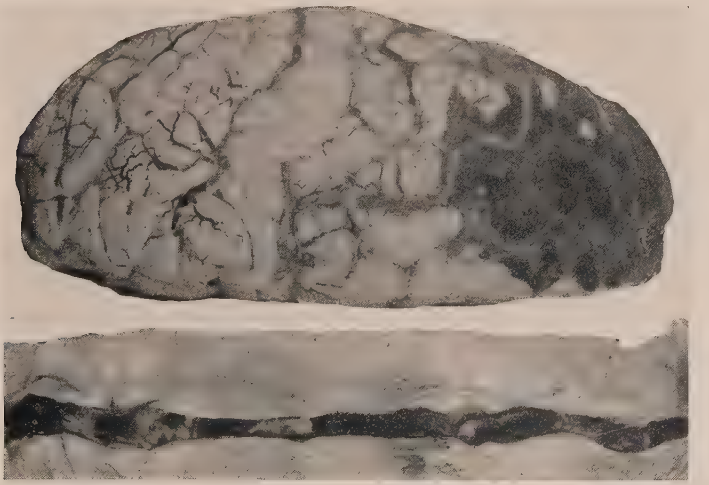

Fig. 6.—Marantic thrombosis of superior longitudinal sinus with resulting hæmorrhage over frontal lobe of brain. Note the greatly dilated and thrombosed cortical veins. The thrombosed sinus is shown below.

It has been found experimentally that there occurs an increased transudation of lymph of low specific gravity into the tissue spaces, owing to the increased filtration pressure, though in normal tissues there is no *œdema,* the excess of lymph being carried off by the lymphatics. Nevertheless, in clinical cases it frequently happens that blocking of a vein is followed by œdema of the limb or part, as the time element and other factors come into play. The relation of venous obstruction to œdema will be considered later (p. 49.) Red corpuscles also not infrequently escape from the engorged capillaries, and in a few situations there may even be gross *hæmorrhage.* For example, when the superior longitudinal sinus is obstructed by thrombus, as occurs sometimes in poorly nourished children, the cortical veins of the brain become enormously dilated, and some of these may give way and cause irregular hæmorrhage in the surface of the brain (Fig. 6). So also, obstruction of a branch of the splenic or renal vein may cause widespread hæmorrhage in the area drained by it, the lesion resembling a hæmorrhagic infarct produced by arterial obstruction. A similar result is seen in the case of the mesenteric veins when thrombosis extends down into the small branches, diffuse hæmorrhage then taking place into the related part of the bowel wall.

Still more serious results follow when there is *interference with the collateral circulation*, as occurs when a portion of the intestine is constricted. In such a case the first effect is interference with the venous return, and as the blood cannot pass off by any side channel, the circulation is brought to a standstill after blood has been pumped into the part through the arteries ; the result is known as *strangulation*. Diffuse hæmorrhage then occurs through the damaged capillaries, and this is followed by gangrene of the part. But in most situations, when a vein is blocked, the blood is carried off from the part by the collateral veins and the circulation through it is maintained, though often at a decreased rate.

(*b*) *Chronic obstruction*. When venous obstruction is of long standing and especially when it is slowly produced by pressure from outside, there often occurs a marked enlargement of the collateral veins, and this may be found either when the obstruction is partial or when it is complete. When, for instance, the inferior vena cava is obstructed by thrombosis or by pressure from a tumour, the epigastric veins may become greatly enlarged and distinctly visible on the anterior abdominal wall; and a corresponding result is seen when there is obstruction to the superior cava, the veins over the clavicle undergoing great development. When there is congestion of the portal circulation, as is common in cases of cirrhosis of the liver, enlargement and varicosity of veins occur, especially at the junction of the portal and systemic circulation, that is, at the cardiac orifice of the stomach and at the lower end of the rectum. In such cases, there may be hæmorrhage from either situation, and, in the case of the cardiac end of the stomach or lower end of the œsophagus, this may be fatal. In chronic portal obstruction there is also considerable enlargement of the superficial abdominal veins. This is sometimes pronounced around the umbilicus, where the dilated veins often present a radiate arrangement giving rise to the so-called *caput medusæ*. Ascites is a frequent result of chronic portal obstruction, as will be described later.

HÆMORRHAGE

The occurrence of hæmorrhage from the large vessels by rupture as the result of injury or disease, is readily understood and examples will be given later. We shall consider here only the multiple hæmorrhages which may occur in various general conditions, and which are often of the nature of minute capillary hæmorrhages or *petechiæ*, though sometimes also of a more diffuse character. Observations on the circulation during life show that in inflammatory and other conditions, an escape of red corpuscles may take place through the capillary walls without permanent rupture, and this is called *hæmorrhage by diapedesis* as contrasted with the hæmorrhage due to actual rupture or *rhexis*. Multiple petechiæ are probably produced in this way in most cases, and the escape of blood is apparently the result of damage to the capillary endothelium. Such hæmorrhages occur in two main groups of conditions. (*a*) In the first place, they are met with in *acute infections* such as septicæmias, scarlet fever, yellow fever, etc., chiefly in the skin and serous surfaces, although bleeding may take place also from mucous membranes. This occurs in the stomach, for instance, in yellow fever and also in various septic conditions, without any discoverable breach of the mucosa to account for it. Multiple hæmorrhages occur also in phosphorus poisoning. (*b*) The second group of conditions in which hæmorrhages are common, includes various *blood diseases*—pernicious anæmia, leukæmia, purpura, scurvy, hæmorrhagic disease of the newly born, etc. Here, again, the hæmorrhages are often multiple and there may be small or more serious bleedings from mucous membranes. The intimate cause of hæmorrhage in the conditions mentioned is imperfectly understood. In infections, hæmorrhages are occasionally produced by the actual presence of organisms ; for example, we have found plugs of the organisms in the capillaries in cases of meningococcus and pneumococcus septicæmia. As a rule, however, they are apparently due to toxæmia. Fatty degeneration may be present in the capillaries in phosphorus poisoning and anæmias, but in most cases of spontaneous hæmorrhage no lesion can be found. In anæmias and purpuric conditions, the occurrence of hæmorrhage is often associated with diminution of the blood platelets and a prolongation of the bleeding time.

There is also evidence that vitamin deficiency is concerned in the occurrence of multiple spontaneous hæmorrhages. Deficiency in vitamin K which produces a hæmorrhagic disease in chickens may play a part in human disease (p. 634). In scurvy too a hæmorrhagic tendency is due to vitamin C deficiency (p. 487).

LOCAL ANÆMIA—ISCHÆMIA

This condition results from interference with the arterial supply, and such interference varies, of course, in degree. We shall first consider the effects of *complete* obstruction, which may be produced artificially by ligature, or may be the result of some pathological condition. Thus, as examples of the latter :—

(*a*) An artery may be plugged by a piece of thrombus ; this may be formed locally at the site of obstruction—as in ordinary *thrombosis*, or it may be carried from some other part of the vascular system, that is, the obstruction may result from *embolism.* A malignant growth also may obstruct an artery either by its local growth or by embolism.

(*b*) Occasionally an artery may be closed by proliferative changes in the intima, though such an occurrence is practically confined to the smaller vessels, and even in them the process is commonly completed by thrombosis.

(*c*) Sometimes excessive contraction of an artery may be sufficient to bring about the effects of obstruction. For example, in Raynaud's disease gangrene of parts of the extremities may occur from this cause, and a similar result is seen in chronic poisoning by ergot, produced by the action of the drug on the walls of the arteries.

By far the commonest and most important causes of arterial obstruction, however, are thrombosis and embolism.

Results of Arterial Obstruction. Establishment of Collateral Circulation. The general statement may be made that in all cases when an artery is obstructed by any of the causes mentioned, there is an attempt to establish a *collateral circulation*, and, in the case of arteries of the limbs and trunk, this is usually successful. In the internal organs, however, as we shall see, the anatomical arrangements of the vessels in many instances do not allow a sufficient anastomotic supply, even under healthy conditions ; and thus serious results follow. When an artery, say of a limb, is suddenly obstructed in a healthy subject, there is a marked sudden drop in the blood pressure in the artery beyond the obstruction and in the branches arising therefrom, and the circulation is brought practically to a standstill ; the arteries then contract and the part contains less blood than normally. Soon, however, the anastomotic arteries undergo an active dilatation and the blood makes its way into and distends the vessels of the affected part. A flow of blood is thus gradually established through the latter, and this increases until ultimately the circulation is sufficiently restored to keep the part alive. Thus the femoral in a healthy subject may be ligatured without permanent damage resulting. The limb becomes cold and somewhat benumbed, and some time elapses before the pulse is again detectable at the ankle ; and it is much longer before complete muscular power is restored. The collateral vessels have, of course, to remain dilated in order to maintain the circulation, and in response to the maintained increased pressure within them structural changes follow. There occurs a thickening of the wall, with increase of the muscular and elastic tissue to correspond with the enlarged lumen ; in other words, the collateral vessels become *permanently enlarged or hypertrophied.* We have a striking instance of great collateral enlargement during the process of development, in the rare congenital condition of stenosis, or even of complete closure, of the aorta beyond the arch (p. 368). In such conditions there occurs a great enlargement of the anastomoses from the vessels of the head and neck, so as to provide a blood supply for the trunk and lower parts of the body.

The development of an efficient collateral circulation, depending as it does on an active dilatation of the anastomotic arteries, presupposes a comparatively healthy condition of the artery walls, and is of course aided by a satisfactory state of the cardiac action. If, however, the arteries are the seat of disease—are atheromatous, fibrosed or calcified—they are often unable to dilate sufficiently to supply the necessary amount of blood to the part, and a varying amount of necrosis will follow. Thus it happens from this cause that in old people the blocking of the main artery of a limb, or even of a large branch, may be followed by death of the part supplied by the obstructed vessel, the condition of senile gangrene resulting (p. 136).

Serious results may follow also when the obstruction is multiple or of spreading character. This is well illustrated in thrombo-angeitis obliterans (p. 306), in which disease thrombosis may occur in many arteries and lead to gangrene even in young adults.

Infarctions. As has been mentioned, in the case of certain arteries of internal organs anastomosis is imperfect, and the obstruction of them is always followed by serious results. Such arteries were specially studied by Cohnheim, who gave to them the name of 'end-arteries.' The term, however, must not be used in a strictly anatomical sense to indicate that there is no anastomosis, but only in the sense that, when obstruction occurs, the circulation cannot be satisfactorily restored by collaterals. With this meaning of the term we may say that an 'end-artery' may have (*a*) no anastomosis, e.g. the splenic artery, (*b*) only capillary anastomosis, e.g. the branches of the renal artery, or (*c*) arterial anastomosis, but insufficient to keep the part alive, e.g. the superior mesenteric artery. We shall treat these anatomical varieties together, and we may state that the obstruction of such a vessel leads usually to (*a*) interference with the nutrition of the part and necrosis, and (*b*) certain circulatory disturbances—congestion and hæmorrhage. The term *infarction* is applied to the altered area which has had its blood cut off, and infarctions are of two main types, viz. the *pale* or *anæmic* and the *red* or *hæmorrhagic*. Occasionally, however, an infarction may be red from dilatation of blood vessels without being hæmorrhagic, for example in the liver, as the result of blocking of a branch of the portal vein (p. 27). Pale infarctions occur in organs where there is little or no free anastomosis, e.g. heart and kidneys; while in organs where there is a freer anastomosis, e.g. the intestine, or a double circulation, e.g. the lungs, red infarctions are found.

Infarctions are usually the result of embolism, the common source of the emboli being vegetations on the heart valves, and are often multiple. Infarction, however, may sometimes be due to local arterial thrombosis, for example in the kidneys in puerperal eclampsia, polyarteritis nodosa, etc., as will be described later.

Infarct or infarction means a stuffing-in, and the name was originally applied to the hæmorrhagic type, as the part appeared stuffed with blood. When, however, pale infarcts were found to have a similar causation, the term was applied to them also. In the case of the brain, the term *softening* is applied to the results of arterial obstruction, as softening is the main occurrence, but the changes which take place are essentially of the same nature as those in infarction as ordinarily understood.

Sites and Characters of Infarctions. In the case of the *brain*, obstruction of the deep nutrient branches passing into and supplying the inner parts of the brain always gives rise to softening, which is usually of the pale or anæmic type. Congestion of the collateral vessels around the softening is present at the early stages, but this soon passes off, and there is then general pallor of the part. Occasionally, however, the softening is of a hæmorrhagic type, and the term *red softening* is then applied. There is considerable anastomosis between the cortical arteries, and the obstruction of a branch is usually without effect. An important factor, however, is the state of the vessel walls, as is well illustrated by the varying amount of cortical softening which results from blocking of the middle cerebral artery (p. 728). The central artery of the *retina* is an end-artery, and its obstruction causes necrosis, with, of course, loss of sight in the eye. Obstruction of a branch of a coronary artery of the *heart* gives rise to an infarction of the muscle; it is usually somewhat irregular in form, implicates especially the inner part of the heart wall, and is of the pale variety though congestion and hæmorrhage are present at the margin. The branches of the *pulmonary artery* have little anastomosis, although blood may reach the part from the bronchial arteries. Infarction due to obstruction of a branch of a pulmonary artery is often met with, and is of the red or hæmorrhagic type; it does not, however, invariably occur when an arterial branch is blocked (p. 29).

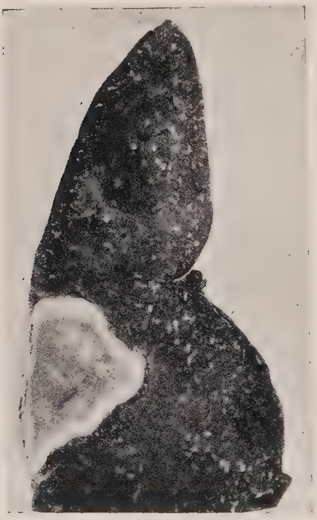
Fig. 7.—Pale Infarction of Spleen, showing Process of Decolorisation at the Margin.

Infarctions of the *spleen* are of common occurrence from obstruction of the arterial branches. They are usually of a pale reddish colour at first, but soon become yellowish when necrosis takes place (Fig. 7);

occasionally they are of the hæmorrhagic type. In the *kidneys*, infarctions are of the pale variety, with a deep red periphery due to congestion and hæmorrhage. The pale portion involves chiefly the cortex, whilst the corresponding part in the medulla is usually red and hæmorrhagic (Fig. 8). When the infarction is of small size it may be hæmorrhagic throughout. These statements apply to the infarctions ordinarily met with at post-mortem examinations. The experiments of Greenfield and others show that after an arterial branch in a kidney is blocked, the area supplied becomes at first swollen and red throughout owing to general congestion. Thereafter, the area becomes pale, and it would appear that the kidney cells in process of dying take up water and the swollen tissue expresses blood from the part, which is thus rendered anæmic and pale. At the periphery and in the medulla the hyperæmia and stasis persist, the nourishment of the capillary walls is impaired, and then hæmorrhage occurs into the tissues. The fact that infarctions met with in the kidney are usually of the pale variety is apparently due to the transitory nature of the early congested stage.

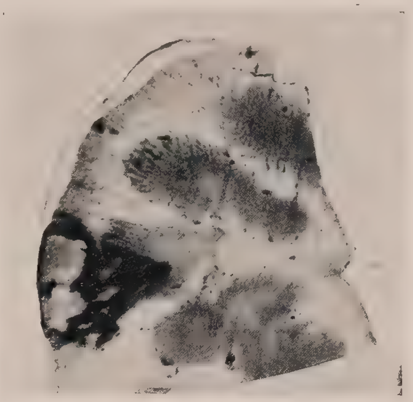
FIG. 8.—Infarction of Kidney, showing pale Necrotic Centre with Hæmorrhagic Margin.

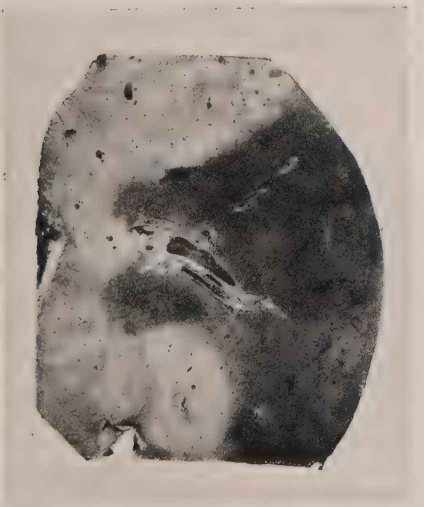
FIG. 9.—Red Atrophic Infarct of Liver, due to Plugging of Branch of Portal Vein; thrombus is seen in the vein.

Blocking of the *superior mesenteric* artery produces a hæmorrhagic infarction of the bowel, which is almost co-extensive with the distribution of the vessel (*vide infra*), and fatal result follows. Obstruction of the inferior mesenteric artery, though the infarction is less complete, may likewise be fatal. In the *liver* a red infarction often follows obstruction of a branch of the portal vein, but necrosis does not occur, owing to the supply of blood from the hepatic artery. The obstruction produces a stagnation of the blood flow in the area affected; the capillaries become widened and the liver cells atrophied—hence the red colour (Fig. 9).

Changes in Infarctions. We have now to consider the effect on the tissues supplied by the obstructed vessel. As we have said, the common effect is *necrosis*, but this is usually not equal in extent to the area supplied by the vessel, on account of a certain amount of collateral anastomosis. The necrosis is usually of the coagulative type (p. 129), though in the case of the spleen and heart, autolytic softening of the infarction sometimes occurs. In the central nervous system the necrosis is attended by softening, as has been stated; that is, it is of the colliquative variety. In connection with the extent of the necrosis, a very important point is the surviving power of the tissues, as evidenced by the time during which they can withstand deprivation of nourishment. In the case of closure of a main cerebral artery, e.g. the middle cerebral artery, where there is considerable cortical anastomosis, the area of softening is not nearly equal in extent to that supplied by the vessel, and the more healthy the vessels the smaller is the cortical softening. And if it were not for the fact that the brain substance can survive deprivation of blood for only a comparatively short time, it would be smaller still; but the necrosis occurs before the collateral supply of blood is sufficient. Thus it follows that the amount of cortical softening due to plugging of the middle cerebral varies much in different cases. The variation in the resisting power of different tissues is shown also by the extent to which they necrose in any given case. In a recent infarction of the kidney, for example, all the tissues are dead in the central part, but at the margin there is a zone where the epithelium is dead, whilst the connective tissue has survived—that is, an imperfect blood supply may be sufficient for the latter but not for the former.

With regard to the *vascular phenomena*, the zone of congestion at the margin of an infarction is simply an indication of attempt at collateral circulation. Moreover, the latter may, as in the case of the superior mesenteric, allow blood to flow into and distend the arteries, but the blood pressure may be insufficient to produce a satisfactory circulation through them. The nourishment of their walls then fails, the capillaries give way and hæmorrhage occurs. The hæmorrhage may be only at the periphery, as in infarcts of the kidneys, or throughout the area as in the hæmorrhagic infarcts of the lungs (Fig. 11); and where there is only peripheral hæmorrhage, as in the kidney, this would probably extend farther into the part, were it not for the fact that the tissues in process of dying become swollen, press on the capillaries, and render the part anæmic. As already mentioned, a transitory early stage of congestion of the part actually occurs. From various experiments Cohnheim concluded that the excess of blood in infarctions was the result of *reflux* by the veins. This is, however, not tenable as a general explanation, although it may play a part in pulmonary infarctions.

Intestinal Infarction. The sequence of events in the hæmorrhagic infarction of the intestine, following obstruction of the superior mesenteric artery, was fully marked out by Welch and Mall. They found that when this artery is ligatured in the dog, there is first a cessation of the circulation in the part, accompanied by a contraction of the muscular coats of the intestine. The circulation soon begins to be restored, the blood flowing in from the collateral anastomoses, but without pulsation being present. The capillaries and small veins become engorged, but the flow through them is imperfect and irregular. Ultimately stasis occurs and diffuse hæmorrhage follows, the whole part becoming infiltrated with blood. Corresponding with these phenomena, the venous outflow becomes greatly diminished after the ligature ; it then increases somewhat as the flow is re-established, and ultimately falls to a minimum. They found that complete deprivation of blood from 2–4 inches of the bowel leads to hæmorrhagic infarction of the part. We have thus an excellent example of the fact that the collateral arterial supply may be able to fill the part with blood, but insufficient to maintain an adequate circulation.

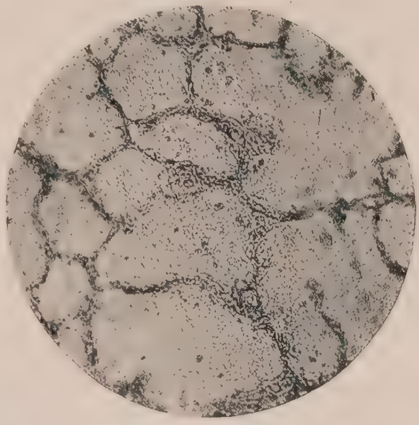

Fig. 10.—Portion of Hæmorrhagic Infarction of Lung, showing Alveoli filled with Red Corpuscles. × 100.

Pulmonary Infarction. It has been stated that hæmorrhagic infarctions are of common occurrence in the lungs (Fig. 10), but infarction does not always follow obstruction of a branch of a pulmonary artery. It has been found experimentally that in healthy dogs embolism in the branches of the pulmonary artery usually does not cause infarction. Further, in the human subject not infrequently the plugging of a fairly large branch is attended by comparatively little or even no infarction. Apparently some other factor, such as malnutrition or abnormal state of the circulation, is necessary for development of a complete pulmonary infarction. Infarctions of the lung are usually met with in cases of cardiac diseases, where pulmonary congestion is present. In such cases the anastomoses from the bronchial arteries are apparently unable to maintain a sufficient circulation in the affected area owing to the raised venous pressure. Possibly reflux from the veins may also play a part. Pulmonary infarction is, as a rule, due to embolism, the embolus usually coming from a thrombus in the right side of the heart, most frequently in the right auricular appendix, occasionally from a thrombus in a systemic vein. Sometimes, however, it results from a locally formed thrombus in a branch of a pulmonary artery, as the artery walls are not infrequently the seat of atheromatous change in long-continued pulmonary congestion (p. 292). Pulmonary infarctions, which are often multiple, are usually conical in shape and have a sharply defined margin (Fig. 11).

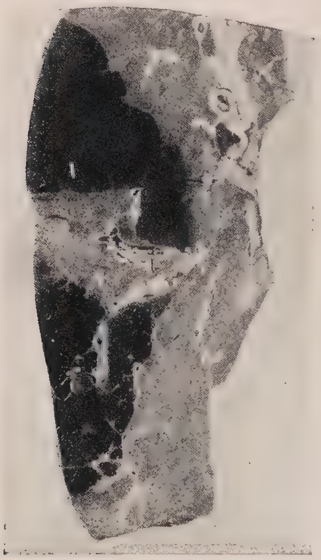

Fig. 11.—Two wedge-shaped Hæmorrhagic Infarctions of Lung. × $\frac{3}{4}$.

Sequels of Infarction. The all-important difference in the results of infarction depends on the presence or absence of organisms in the embolus or thrombus. If the infarction is free from organisms, its dead tissue acts like a foreign body; a zone of connective tissue reaction forms around it, and it becomes enclosed in a capsule (p. 133). A process of slow absorption occurs, and the part undergoes shrinking; ultimately a depressed cicatrix may mark the site of the infarction. When there has been repeated embolism with multiple infarctions, the organ may be puckered and deformed from the scarring; this is often seen in the case of the kidney. Any pigment derived from extravasated blood corpuscles is slowly absorbed, but in the case of hæmorrhagic infarctions, e.g. of the lungs, a brownish colour persists for a long time. Apart from the case of cerebral softening, there is occasionally autolytic softening in infarcts in other organs. Thus an infarction in the spleen may undergo central softening, quite apart from the presence of bacteria, and a similar change may be met with in infarction of the heart wall, the condition known as *myomalacia cordis* resulting. Such occurrences are, however, relatively uncommon. If organisms are present in the plugged vessel, they may extend to the infarction and surrounding tissue, and produce suppuration and abscess; if the organ has a serous covering this becomes infected and inflamed. Such *septic infarction*, as it is called, is common in some types of bacterial endocarditis, suppurative bone disease, etc.; it is, in fact, the essential feature of pyæmia. Occasionally, when putrefactive organisms are present, the infarcts may become gangrenous in character; for example when they occur in the lungs secondarily to putrid thrombosis of veins, e.g. the pelvic veins or a lateral sinus.

Incomplete Arterial Obstruction. This is of frequent occurrence and brings about serious effects of both structural and functional kind. A common general result is to produce starvation atrophy and disappearance of specialised cells with accompanying overgrowth of connective tissue. For example, fibrosis of the myocardium (p. 336) is most frequently produced in this way. In the kidneys the primary effect is on the glomeruli, which undergo hyaline change ; this is an important lesion in primary arterio-sclerosis and again leads secondarily to various degrees of fibrosis. In the brain too, especially in senile states, a patchy sclerosis with disappearance of nerve elements may be brought about in a like manner. In the limbs, various trophic and circulatory disturbances may result from imperfect supply of arterial blood, and after walking a cramp-like pain with inability to progress, ‘intermittent claudication,’ is not an uncommon symptom. These effects, however, are more conveniently considered in connection with the different systems.

THROMBOSIS

Thrombosis is sometimes described as coagulation within the vascular system during life, but, as the process is not always identical with coagulation, it would be better to describe it as *the formation of a solid or semi-solid mass from the constituents of the blood within the vascular system during life.* Thus, a tumour growing into a vein is not a thrombus, although it may sometimes resemble it in appearance. Thrombi may form in any part of the vascular system—heart, arteries, veins or capillaries. They vary considerably in appearance and are often classified as *red*, *pale* and *mixed thrombi.* The red thrombi are the most rapidly formed, and the process is chiefly one of ordinary coagulation. Pale thrombi are of a firmer consistence and have a dull structureless appearance ; they present various shades of colour, from greyish white to pale red. In the heart, rapidly formed thrombi may have a yellowish colour, owing to their being largely composed of fibrin. Mixed thrombi vary in appearance, according to the rapidity of formation, some parts being pale and slowly formed, others red. Sometimes, especially within aneurysms, paler and darker parts alternate, so that a laminated appearance results (Fig. 17). We shall now give an account of the characters of thrombi as they are met with in various situations, and afterwards discuss their mode of formation.

Sites and Varieties of Thrombosis.

(*a*) *Cardiac Thrombosis.* In the case of the heart, the dark postmortem clots which are nearly always present are, of course, to be excluded. They are, as a rule, uniformly dark and of a soft consistence, and are formed by simple coagulation of the blood after death : occasionally the red corpuscles settle before coagulation occurs, and the upper (that is anterior) part of the clot is yellow and gelatinous. The most rapidly formed thrombi, in the strict sense, are the so-called agony thrombi or clots (Fig. 12). They may occur in both ventricles but are commoner on the right side. They are of a yellowish or pinkish colour and somewhat stringy consistence, usually attached to the muscle at the apex of the ventricles, and they form elongated masses which often extend through the arterial orifices. They are composed chiefly of fibrin with leucocytes and red corpuscles entangled, the fibrin having manifestly been separated out from the blood when it was still circulating; they are not uncommon when death has occurred somewhat slowly, and they are nearly always present on the right side in cases of lobar pneumonia. Thrombi of slower formation occur both in ventricles and auricles. They may be in the form of irregular deposits of reddish colour varying in depth and of a moderately firm consistence; or they may be more rounded and of a pale, sometimes yellowish, appearance. The latter are sometimes known as 'cardiac polypi' (Fig. 13). Such thrombi usually occur in the depressions between the muscular bands and occasionally may show autolytic softening in the centre.

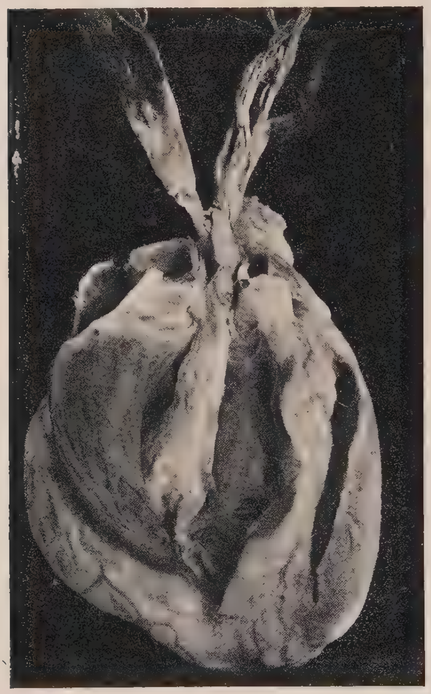

FIG. 12.—Agonal clot in right ventricle extending along the pulmonary artery in a case of pneumonia.

In the ventricles, the commonest site is the apical part of the left ventricle, and in the great majority of cases the thrombi are secondary to fibrous change in the muscle underneath. They may be of large size especially where there is a local dilation. In the auricles, thrombosis is commonest in the appendix, especially on the right side, and is frequently met with in cases of cardiac disease with distension of the auricles. Small globular thrombi also may occur in the auricles; and in mitral stenosis, a

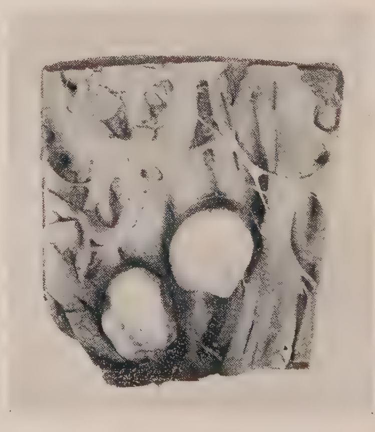

FIG. 13.—Globular Thrombi in Right Ventricle.

so-called 'ball-thrombus,' which may reach more than an inch in diameter, sometimes forms in the left auricle and may lie free. The vegetations which form on the valves in endocarditis are essentially thrombi. In the rheumatic type they appear as minute pinkish-grey

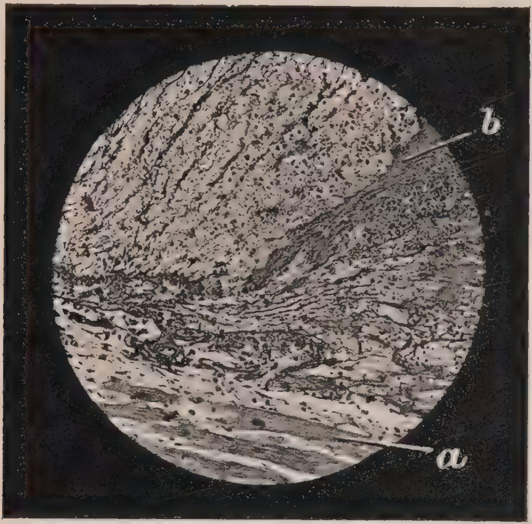

FIG. 14.—Thrombus within Auricle.
(*a*) Heart muscle. (*b*) Thrombus: some parts are loose, others dense.

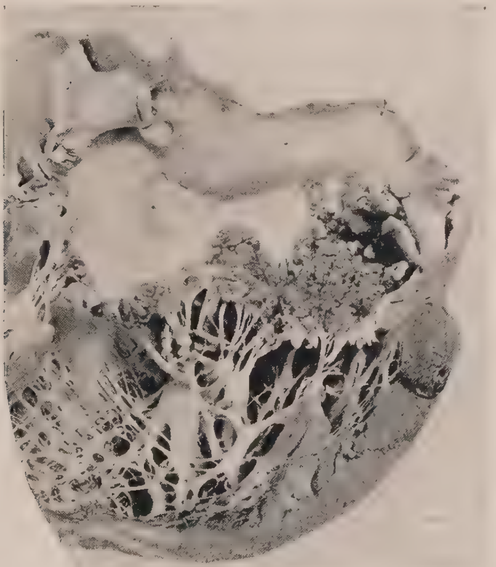

FIG. 15.—Numerous Vegetations (Thrombi) on auricular aspect of Mitral Valve, from a case of Bacterial Endocarditis.

bead-like projections, but in bacterial endocarditis they come to form larger and sometimes crumbling masses (Fig 15.). Their characters will be described more fully later, but the denser vegetations are excellent examples of thrombi very slowly formed over damaged parts of the endocardium.

(*b*) *Arterial Thrombosis.* In the arterial system, thrombosis is commoner in the smaller vessels, as the blood stream is slower in them. The thrombi are usually formed gradually and are of the paler, denser variety. It is noteworthy that the aorta may be the seat of advanced atheroma, with great irregularity of the surface, without the occurrence of any thrombosis. Sometimes, however, thrombus formation may take place over a roughened patch, especially when, at the same time, there is a depression (Fig. 16). The conditions of occurrence in the arterial system clearly point to the importance of the rate of the blood stream as a factor. Within an aneurysmal sac some amount of thrombus is the rule, and, as has been said, the thrombus has often a laminated character and occasionally may come to fill the sac (Fig. 17).

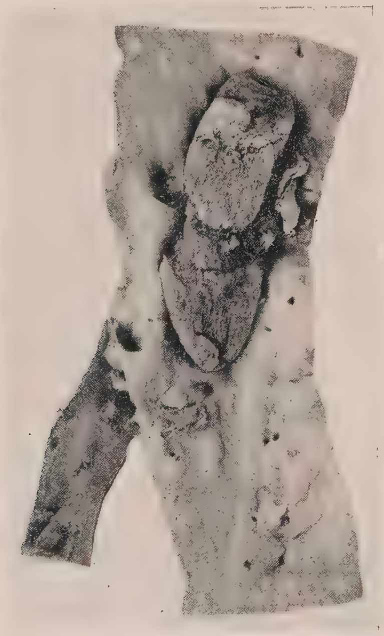

Fig. 16.—Atheroma of the Aorta with extensive Thrombus Formation over the origin of Superior Mesenteric and other Arteries. Infarction of intestine resulted.

(*c*) *Venous Thrombosis.* Thrombosis in the venous system is commoner than in the arterial, even although the former is less affected with disease; the slowness of the blood stream in a vein is here the important factor. The site is often in connection with a valve or some thickened patch in the initma. The thrombus in its initial stage is slowly formed and is of pale colour and dense consistence. In its subsequent growth, which takes place more rapidly, it is composed of pale trabeculæ or laminæ with red coagulum between; these extend outwards from the wall of the vessel, and ultimately lead to occlusion of the lumen. The thrombus thus formed has a reddish appearance and is often an oval mass which has been compared to a serpent's head projecting in the direction of the blood flow. When the vessel is occluded, a dark red thrombus is formed distally by a process of ordinary coagulation and extends for a varying distance (Fig. 18). Within a vein such as the femoral, the whole thrombus may measure several inches in length. Such a thrombus may become detached and carried to the lungs, giving rise to fatal pulmonary embolism. In many cases of venous thrombosis its occurrence is traceable to some local lesion of the wall or to the spread of some pathological process from outside. Thus it occurs when the vein is involved in a chronic inflammatory process, when it is pressed on or invaded by tumour, and above all when a septic inflammation reaches it. In the last-mentioned case the thrombus may be invaded by organisms and become the seat of suppurative change. Thrombosis in veins is, however, also common in various conditions of infection or malnutrition, often without manifest local lesion to originate it. It is met with, for example, after fevers, especially typhoid, after child-birth, and it was not uncommon in chlorosis.

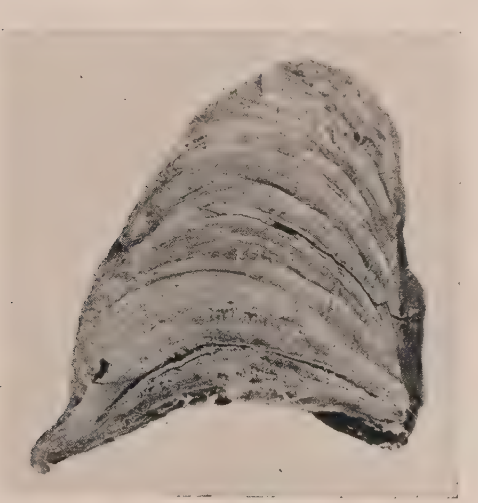

Fig. 17.—Laminated Thrombus from Aneurysmal Sac.

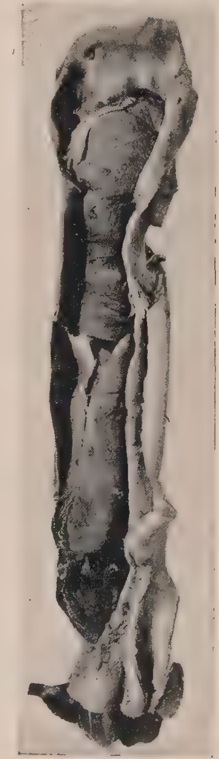

Fig. 18. — Large Thrombus in Inferior Vena Cava, with rounded projection at upper end.

Another important form is that met with after operations—*post-operative thrombosis.* Its commonest site is an iliac or femoral vein and its branches, more frequently on the left side ; and it may be a formidable complication, as not infrequently the thrombus becomes detached and results in fatal pulmonary embolism. The thrombosis occurs especially after operations on the abdominal and pelvic organs ; it is relatively rare after operations on the upper part of the body. Occasionally the process of thrombosis can be traced from the site of operation, but usually it starts quite apart from it in the large veins mentioned. It may occur in aseptic cases, though it is more frequent in septic conditions. Slow rate of blood flow undoubtedly plays an important part but a definite etiology often cannot be assigned (*vide infra*).

In poorly nourished children thrombosis may occur in the superior longitudinal sinus, and may give rise to hæmorrhage on the surface of the brain (p. 21). This variety is sometimes called *marantic thrombosis*. A tendency to thrombosis is noted also in chronic cardiac cases with venous congestion and in conditions of cachexia, for example that due to cancer.

(*d*) *Capillary Thrombosis*. Thrombi form also in capillaries when their walls are much damaged or actually necrosed, e.g. in severe inflammation. They are usually composed of red corpuscles which are fused together into homogeneous masses, whilst the scanty plasma between them has coagulated.

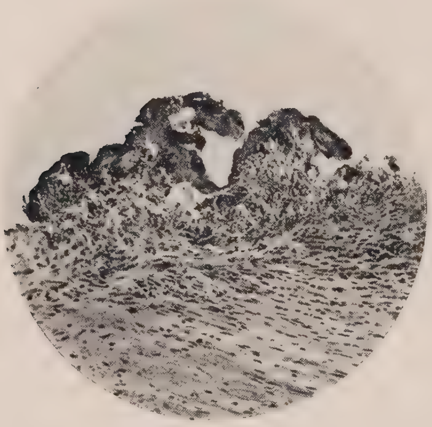

Fig. 19.—Early vegetation on aortic valve showing deposit of hyaline material on the surface with early organisation. (Dr. A. C. Lendrum.) × 100.

These facts with regard to different kinds of thrombi in the human subject suggest that in their formation the chief factors concerned are (*a*) abnormality in the vascular endothelium, (*b*) slowing or stagnation of the blood stream, and (*c*) possibly some altered blood states. This question will now be considered.

Causation of Thrombosis. We have now to consider the exact structure of thrombi and experimental evidence as to their mode of formation. If we examine a pale and dense thrombus, that is, a slowly formed thrombus, we find that it is composed essentially of homogeneous or slightly granular structureless material, in which only a few leucocytes may be present, though in spaces or fissures in the material they may be abundant (Fig. 20). When the thrombus has been formed less slowly, as in a vein, the dense material is often arranged in trabeculæ or laminæ so as to give a sort of coralline appearance, and leucocytes are often seen adhering to the surface of these in large numbers. In the spaces between the trabeculæ a reticulum of fibrin varying in density is present, and its meshwork is filled with red corpuscles along with a certain number of leucocytes (Fig. 21). The nature of the material constituting the denser trabecular portions of the thrombus was for long the subject of discussion, but it is now known to be essentially composed of fused blood platelets. Some of the dense material, however, may be altered fibrin which has become homogeneous in appearance, as we know that a similar change may occur in fibrin in old inflammatory exudates. In the process of thrombosis generally, it may thus be said that the first occurrence is deposition of platelets which become agglutinated and fused together. The subsequent structure of the thrombus depends mainly on the rate of blood flow. If this is rapid, as in an artery or over a heart valve, the thrombus is mainly formed by the progressive deposition of platelets ; if it is less rapid, as in a vein, the deposition of platelets leads to the formation of trabeculæ or laminæ which grow out from the vessel wall and to the surface of which leucocytes adhere. From the platelet masses thrombokinase is diffused, which leads to coagulation in the interspaces. Finally, when the blood flow is brought to a standstill, a dark red thrombus is formed with relative rapidity and is mainly the result of ordinary coagulation.

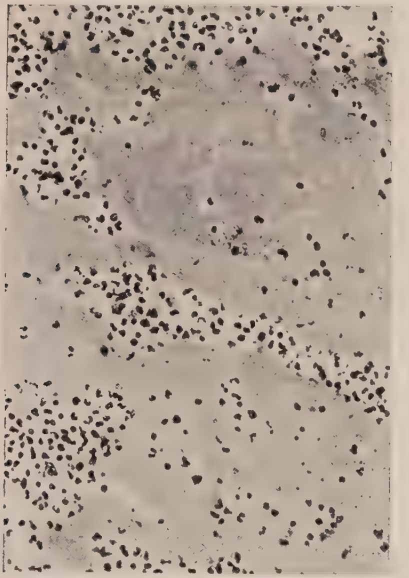

Fig. 20.—Portion of pale Thrombus, showing dense Masses of Granular Material, composed of fused Platelets, with Collections of Leucocytes between. × 250.

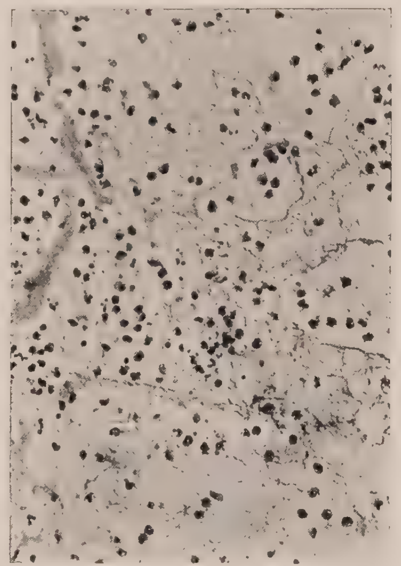

Fig. 21.—Portion of red Thrombus, showing Reticulum of Fibrin with Leucocytes and numerous Red Corpuscles between. × 250.

The part played by the platelets in thrombosis depends mainly on the sticky or adhesive character which they assume when blood is shed, or when they are brought into contact with an abnormal vascular lining. In fact, this change is brought about by the same conditions as those which give rise to coagulation, and there is evidence that a thrombokinase is formed. Eberth and Schimmelbusch showed that, in normal states of the circulation, the platelets circulate along with the red blood corpuscles, with which they mingle freely. If, however, the stream is gradually slowed, a point is reached when they fall out into the peripheral zone and come in contact with the vessel wall. Any local dilatation leads to eddy or whorl in the stream, and in this case also there is a falling out of the platelets. These observers found that if a vessel wall were merely damaged, e.g. by a caustic, thrombosis might not occur, but if at the same time the damaged part were projected inwards, the platelets were brought into contact with its surface to which they adhered, heaping themselves up and in this way starting a thrombus. Their general conclusion accordingly was that the two important factors in thrombosis are (*a*) damaged endothelium which brings out the adhesive properties of the platelets, and (*b*) some condition of the blood flow which brings the platelets into contact with the damaged surface. This conclusion is accordingly in agreement with what is to be observed in the human subject, as described above. It is to be noted that, although the platelets may be concerned in coagulation itself, for which there is clear evidence, the thrombus at an early stage is simply formed by the massing together or conglutination of the platelets, and not by a process of coagulation, although the latter may occur secondarily.

With regard to the occurrence of thrombosis in general, it may be said that in the great majority of cases the starting-point is either some lesion of the vascular intima or of the endocardium. In all such conditions, the local lesion, aided often by a slow blood stream, affords a satisfactory explanation of the thrombosis. But in many cases the causation is obscure. This is so in thrombosis occurring in such states as marasmus, fevers, chlorosis, also in post-operative and post-partum thrombosis. Bacteria have been found in such conditions, and invasion of the intima by them may be the immediate cause; whilst in various fevers small collections of leucocytes have been detected in the intima of vessels, and the presence of these is an indication of damage to the wall, which may possibly be produced by toxic action. Again, certain bacterial products may tend to promote coagulation. The *Staphylococcus aureus*, for example, produces a coagulase which has a striking effect in accelerating and intensifying clotting. But such explanations cannot be justifiably applied in all cases. In view of this fact, a number of observers hold that thrombosis may occur simply as the result of stagnation of the blood, and they accordingly speak of *static thrombosis*. It must be admitted that abnormal slowness of the blood stream is an important contributory cause, and will act especially when the lower part of the body is immobilised; and we may say also that in many instances thrombosis would not have occurred had such stagnation not been present. But even with a slow blood stream, provided that the vascular intima is healthy, there is no evidence, experimental or otherwise, that the formation of a thrombus may occur. It seems to us that we must assume in such cases the presence of some local lesion of the intima, which may be the result of a mild infection, malnutrition or toxic action. Its nature, however, is often quite obscure.

We may mention that in certain forms of snake poison, extensive thrombosis, or rather coagulation, occurs in the vascular system, but there is nothing quite analogous to this in the case of human disease. There is no evidence that leucocytes play an important part in the formation of thrombi, although at places they may occur in considerable numbers, in crevices or entangled in the fibrin. In leukæmia, however, where the leucocytes are in great excess, they may accumulate in masses, and lead to obstruction. In this case we may speak of *leucocyte thrombi*. Secondary invasion of the blood by bacteria is common in this disease, however, and it appears likely that they may be the means of starting the formation of the thrombi.

Sequels of Thrombosis. The normal occurrence may be said to be the process of *organisation*. The thrombus becomes permeated by young connective tissue cells and capillaries, the latter growing in from the vasa vasorum and from the intimal endothelium; its substance becomes gradually absorbed and ultimately replaced by connective tissue. In some instances the young vessels which grow in from the endothelium covering the thrombus anastomose, and then undergo enlargement; in this way a new channel may be formed and the thrombus is said to be canalised. The restoration of the channel may occur also from a shrinking of the thrombus (p. 114). The process of organisation requires a comparatively healthy state of the vessel wall, and when the latter is the seat of disease, e.g. is fibrosed or calcified, there may be little or no organisation; in this case the thrombus may become inspissated, shrink somewhat, and at a later period become calcified. A hard calcareous mass or phlebolith may thus form in a thrombosed vein. In certain cases thrombi may become infected with pyogenic organisms and may undergo softening by their action. A thrombus in a vein, for instance, may thus undergo suppuration, and portions may be carried by the blood stream and give rise to abscesses in other parts of the body; pyæmia, in fact, is often produced in this way (p. 182).

Although thrombosis often leads to serious effects, it has also, in certain cases, a *protective* function. When an ulcerative process, for instance, reaches a vessel and destroys the wall, thrombosis within the vessel may prevent the occurrence of hæmorrhage; so also when there is organismal invasion of a vein with suppuration, the thrombosis which extends beyond the part invaded by the organisms may sometimes act as a barrier to their entrance into the circulation. This is well illustrated in the case of suppurative thrombosis in the sigmoid sinus, where pyæmia occurs only occasionally, since ordinary thrombosis usually extends beyond the actual suppuration.

EMBOLISM

By embolism is meant the transference of abnormal material by the blood stream and its impaction in a vessel. The material which is called an *embolus* may be of various kinds. In the great majority of cases, it is a portion of a thrombus or of a vegetation on a heart valve; occasionally material from an ulcerated atheromatous patch. A portion of a tumour may form an embolus, and, in the case of the capillaries, there may be embolism by bacteria, fat globules, air globules or collections of parenchyma cells. The site of embolism will, of course, depend on the source of the embolus. Thus, for example, embolism of the pulmonary arteries and their branches is secondary to thrombosis in the systemic veins or in the right side of the heart. It is to be noted, however, that in some instances where there has been a patent foramen ovale, an embolus has passed from the right side of the heart to the left auricle and thence been carried to the systemic circulation; such a condition has been called *crossed* or *paradoxical embolism*. With this exception, the emboli occurring in the systemic circulation are derived from thrombi on the left side of the heart, from vegetations on the aortic and mitral valves, and occasionally from thrombi in the aorta or large vessels or from portions of atheromatous patches. In the case of emboli carried from branches of the portal vein, the embolism of course occurs in the portal branches in the liver.

Effects of Embolism. As regards the effects of embolism, a distinction between bland or aseptic emboli and those containing organisms is of great importance. (*a*) In the case of the former, the results are simply those of mechanical plugging and will vary according to the site of the embolus. These effects have already been fully described in connection with arterial obstruction. Thus infarctions in various organs, softening in the brain, etc., are produced (p. 26). A specially important form, however, is the *pulmonary embolism* resulting from the detachment of a thrombus in a large vein, usually the femoral. It occurs most frequently about the tenth day after operation, although both before and after that time. Such thrombi form in conditions which have already been described (p. 35) and in any of them pulmonary embolism may result. It is a not uncommon event after operation and leads to a fatal result in patients who are apparently doing well. As has been indicated, the thrombus is of considerable length and it may become separated *en masse* and carried to the right side of the heart, causing a sudden blocking of the pulmonary trunk or one of its divisions. The result is often rapidly fatal, death occurring at once or after a varying period of pulmonary distress. The thrombus is sometimes so long that it is found *post mortem* coiled up like a snake in the right ventricle with one end extending along the pulmonary artery (Fig. 22); or the thrombus may be contained within the pulmonary artery or its branches. When the patient has lived some time after the embolism, a varying amount of hæmorrhagic infarction may be present in the parts supplied by the blocked vessels. Infarction, however, is never co-extensive with the area of distribution, and sometimes there is none. Pulmonary embolism is rare in children (Blacklock). This rather suggests that the occurrence of the initial venous thrombosis from which the embolus arises is due to minor lesions in the venous intima which develop as age advances.

(*b*) If the emboli contain bacteria, suppuration may follow; this is the ordinary method in which multiple abscesses are produced in pyæmia. In other cases, without actual suppuration there may be inflammatory change, for example fibrinous exudation on the surface of an infarct. An infective embolus, when arrested in an artery, occasionally weakens the wall and gives rise to an aneurysm—*mycotic aneurysm* (p. 312). In various septicæmic and pyæmic conditions, the capillaries may be seen to be completely plugged by organisms, most frequently micrococci, the appearance being as if embolism of bacteria had occurred, but in such conditions, what usually happens is that either a few organisms settle on the endothelial surface and then grow so as to fill the capillary; or, on the other hand, a small portion of a thrombus carrying the organisms becomes impacted and the organisms then grow along the capillaries.

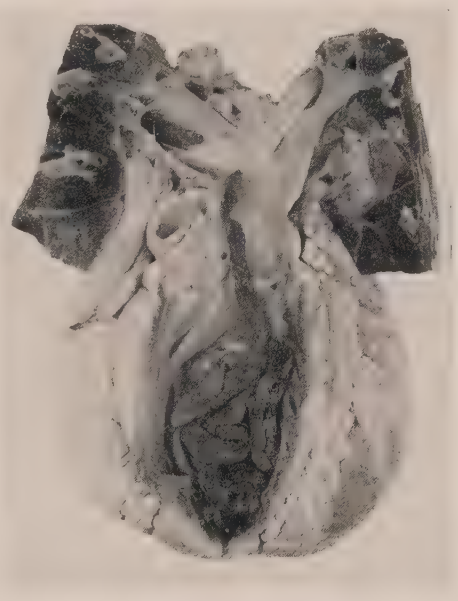

FIG. 22.—Pulmonary Embolism; Heart showing large cylindrical Embolus in Right Ventricle extending up into Left Pulmonary Artery.

Embolism from tumours is of two kinds. A few cells of the tumour may gain access to the blood stream and form an embolus in a capillary in some distant organ. This is the method by which secondary growths ordinarily occur by means of the blood stream. In other cases there may be actual growth of a tumour into a large vein, and a portion of this may become detached, carried by the blood, and impacted in a vessel, usually a branch of the pulmonary artery or of the portal vein.

Fat Embolism. The entrance of fat into the circulation occurs as the result of laceration of a vein surrounded by adipose tissue, and its commonest cause is fracture of a long bone with laceration of the fatty marrow. It has been observed after laceration of adipose tissue generally, or of a fatty liver ; also in caisson disease. It is stated to occur, to a certain extent, also in inflammations of tissues rich in fat. Probably in every case of fracture of bone fat enters the circulation, but it is only occasionally that it gives rise to symptoms, and a fatal result is rare. In fatal cases, the fat is found to be present in large quantities in the form of globules in the small arteries and capillaries of the lungs, whilst there are usually marked œdema around and also scattered hæmorrhages. Death appears to result chiefly from mechanical plugging of the pulmonary capillaries, and the chief symptoms are of pulmonary nature. A certain amount of fat may pass into the systemic circulation and embolism may occur in other organs (Fig. 23). In the brain small hæmorrhages have been found in some instances.

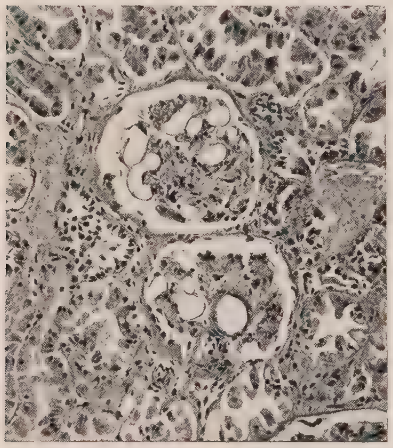

Fig. 23.—Fat embolism of glomerular capillaries in a case of caisson disease. The fat appears as unusually large clear globules. (Dr. A. C. Lendrum.) × 125.

Air Embolism. This takes place when air is aspirated into an open vein, especially a large vein near the heart ; though the frequency and seriousness of the condition have probably been exaggerated. The air may produce effects in two ways. It may become mixed with the blood in the right ventricle, forming a frothy fluid, and thus may interfere with the proper emptying of the cavity, or, again, the bubbles of air may become arrested in the pulmonary capillaries and lead to the mechanical effects of embolism. When air enters the circulation it becomes absorbed with relative rapidity, and it would appear that the sudden entrance of a considerable amount is necessary to produce serious results. Experiments have shown that animals vary much in their susceptibility to the entrance of air. Rabbits, for example, are comparatively susceptible, whilst dogs can tolerate the entrance of large quantities without serious effects ; the human subject is said to occupy an intermediate position. It is to be noted that bubbles of gas may be found in the blood after death, which are due to the action of a particular organism, viz. the *Bacillus ærogenes encapsulatus* or *B. welchii*, and it is likely that cases of this kind have sometimes been described as air embolism.

Parenchyma Cells as Emboli. In certain conditions special types of cells form emboli, especially in the pulmonary vessels, and may be recognised by their characters. As examples, we may mention the megakaryocytes or giant-cells of the bone marrow in cases of fracture of bone and in severe infections; the syncytial cells from the placenta, first observed in cases of eclampsia but afterwards found to occur in other conditions; and liver cells after laceration or necrotic lesions of the liver. Such cellular emboli lead to little result, the cells in all probability merely undergoing absorption.

ŒDEMA OR DROPSY

By these terms is meant *an excessive accumulation of fluid in the connective tissue spaces or serous sacs of the body.* When this occurs in the skin and subcutaneous tissue, the part is swollen, puffy, and pits on pressure; in the case of the serous sacs large collections of fluid may form. The term œdema may be used as synonymous with dropsy, though it is sometimes restricted to dropsy of the solid tissues and organs. Other terms are employed according to the site, e.g. *anasarca* when the skin and subcutaneous tissues are affected, *hydropericardium* and *hydrothorax* when the accumulation is in the pericardium and pleural cavities respectively, *ascites* when in the peritoneum. *Hydrocephalus* means an accumulation of cerebrospinal fluid within the ventricles of the brain, but as the fluid and also the mechanism of production are of different character from that in œdema, this lesion will not be included in the present account. In the case of œdema of the lungs, the fluid is present within the lung alveoli as well as in the connective tissue. In œdema the accumulation of fluid is associated with general disturbances of the nutrition of the tissues, and this, as will be explained below, may tend to intensify the condition, a sort of vicious circle being established. It is to be noted that dropsical tissues have a lowered resistance and are prone to bacterial infection, and when this occurs the inflammatory changes may spread rapidly. This is well seen in the case of the serous sacs where inflammation is not infrequently superadded.

The fluid in œdema corresponds generally with ordinary lymph in composition, but there is often a smaller proportion of proteins and its specific gravity is low, usually 1006–12, though figures both below and above this are met with. The fluid ordinarily does not undergo coagulation when removed from the body, but sometimes a loose coagulum forms; coagulation may occur, however, on the addition of fibrin ferment. The separation of fibrin does not take place in an ordinary dropsical fluid in the body. Accordingly, if fibrin formation is present, say, in a serous sac, there must be some other cause than that producing the dropsy. The smallest amount of protein in the fluid is met with in the more chronic type of renal œdema, where it may be only 0·05 per cent. (Fischer and Fodor); as a contrast to this is the fluid in inflammatory œdema, e.g. of the skin, where the percentage of protein may reach a figure not much below that of the blood serum.

Cells are always scanty ; they are chiefly lymphocytes and mononuclears, but swollen endothelial cells also occur. The last mentioned may be in considerable numbers and may occur in small clumps when the fluid is in a serous cavity. These dropsical fluids of low specific gravity are spoken of as *transudates,* in contrast to the inflammatory *exudates,* the specific gravity of which is above 1015, and often considerably so. The distinction is convenient and holds generally, but intermediate varieties are met with, especially in the inflammatory œdemas.

We may mention that there is also a dropsy or œdema of cells (p. 142)—a condition in which they become swollen up owing to imbibition of water. And we may add that in ordinary œdema, especially when it is of long standing, the formed elements, e.g. the collagen fibres, seem to attract water, and they may become swollen in appearance and less defined. Sometimes this is a marked feature, the tissue becoming rather gelatinous than water-logged and not pitting on pressure ; the term ‘ solid œdema ’ is then applied. It may also be noted that there has to be a considerable addition of water to the tissues before distinct pitting is noticeable. Lewis found, for example, that the volume of a limb might increase 10 per cent. before this occurred. In clinical cases of general œdema there is accordingly a stage when there is an increase of body weight before recognisable œdema actually appears.

Varieties of Œdema. Before considering the mechanism of production of œdema, it will be convenient to state shortly the main types of the condition met with clinically. Œdema may be *general,* or at least widespread, or it may be *local.* General œdema is met with in certain types of cardiac and renal disease, and is named accordingly.

Cardiac Œdema is apt to occur in cases of long-standing general venous engorgement. It appears first of all in the most dependent parts of the body and gradually extends upwards. Thus it is usually noticed first round the ankles, and pitting may be elicited by pressure over the lower end of the tibia. When the condition is advanced, the limbs become greatly swollen and water-logged, while the skin is tense and vesicles may form. Accumulation of fluid may occur also in the serous sacs. When the patient is in bed, the influence of gravity is again manifest. In this, as in all forms of œdema, the fluid collects more readily in the looser tissues, and the external genitals tend to be markedly affected. We thus see that in cardiac œdema the two main factors concerned are (*a*) general venous congestion, and (*b*) gravity, i.e. hydrostatic pressure. It is to be noted, however, that general venous congestion may exist for a long time before the onset of œdema.

Renal Œdema. This may be met with (*a*) early in the course of acute nephritis, often appearing suddenly. But the more extreme examples are seen (*b*) at a later stage in certain cases of subacute nephritis, ‘wet nephritis,’ and in nephrosis ; it is then associated with albuminuria and usually with oliguria. In primary renal fibrosis (p. 670), renal œdema is absent unless a more acute condition is superadded ; but œdema may occur at a later period as a result of secondary dilatation of the hypertrophied heart, and then presents the features of cardiac œdema, as described above. The distinguishing features of true renal œdema are that its distribution is general throughout the body and is less determined by gravity, its amount in different parts depending chiefly on the looseness of the tissues. In acute nephritis it is usually noticed first in the tissues of the face, especially round the eyes, where it gives rise to swelling and an appearance of puffiness. Later, it may become more marked or may subside. The œdema of subacute nephritis and of nephrosis (p. 661) is often of marked degree, involving not only the superficial structures, but also the deep parts and internal organs. There is usually a marked fall in the blood proteins with corresponding fall in their osmotic pressure. We may mention further that in this type of renal œdema we meet with the lowest percentages of protein in the transudate. The significance of these facts will afterwards be considered.

Cachectic Œdema or *Dropsy*. This term is convenient from a clinical point of view though it does not really represent a separate variety. In many chronic wasting diseases and anæmias, e.g. cancer, tuberculosis, leukæmia, etc., œdema sometimes supervenes, especially late in the disease, and usually starts in the lower extremities. In many cases cardiac weakness is the prime factor, though it is aided by the anæmic condition and the general malnutrition which will affect both the capillary endothelium and the cells of the tissues. Fall in the plasma proteins, if present, will favour the occurrence of œdema. It is sufficient for the present purpose to recognise that œdema may supervene in many diseases not primarily either cardiac or renal in nature. We may add that a certain degree of effusion into the pericardial and pleural cavities is common in many conditions where death has occurred gradually.

Famine Œdema. An interesting form of œdema was observed on the Continent during the late war, especially amongst prisoners, and is known as ‘famine œdema.’ It is clearly caused by imperfect nutrition, and protein insufficiency seems to be the main factor. Examination of the blood showed a marked fall in glucose, fats and lipoids, and proteins, the last being sometimes reduced to half the normal amount. It seems likely that the hydræmic state of the blood with fall in osmotic pressure of the proteins is the most important factor in the production of the œdema, but it has been supposed that the latter may be the result of increased permeability of the capillary walls due to the state of malnutrition. Famine œdema has been not infrequently associated with xerophthalmia, a condition in which opacity with ulceration of the cornea occurs, and which is regarded as a result of deficiency in fat-soluble vitamin A (p. 829). A form of œdema, somewhat similar to famine œdema, has been observed in infants when there has been excess of carbohydrates in the diet with marked deficiency in other foodstuffs. In all such examples of nutritional œdema, the problem is a complex one, and the factors which we have mentioned may be concerned in varying proportions.

Local Œdema. Of local dropsy or œdema there are several varieties. There is first of all that resulting from obstruction of a vein. For example, thrombosis of the femoral vein is usually followed by œdema of the corresponding limb, the condition known as 'white leg.' Portal obstruction, often caused by cirrhosis of the liver, leads to ascites. This form of local œdema is manifestly related to the cardiac type and will be considered along with it. Obstruction of lymphatics, e.g. by cancerous growth, may sometimes be concerned in the production of local dropsy, as will be described below.

Œdema of the tissues in connection with inflammation and generally known as *inflammatory œdema*, is another form. In the region of a poisoned wound or malignant pustule, the tissues around for a considerable distance may be œdematous and may pit on pressure, and this may occur without the actual presence of the organisms, being produced by the diffusion of the toxins. A similar œdema is often a prominent feature around the bites of poisonous insects and reptiles. In other cases again, for example in the group of malignant œdemas and gas gangrenes, the œdema of the tissues is associated with the actual presence of the causal organisms, though here again it may extend beyond them. Other examples of toxic œdema are urticaria or nettlerash, characterised by the rapid development of patches of local œdema of the cutis, and the slight œdema of the skin which is met with in chronic arsenical poisoning. In all these cases the œdema is the result of poisons acting directly on the capillary walls and tissue elements, and thus in essential nature it is related to the exudate in inflammation. And the œdema of the skin or whealing which occurs as the result of mechanical, chemical or thermal injury is similarly related. As has been already stated, it has been shown by Lewis that such œdema is the result of the release from the damaged tissues of a substance with histamine-like action—the so-called H-substance (p. 13).

Œdema due to Lymphatic Obstruction. When the thoracic duct is obstructed, as may result from malignant growth or tubercle, or in cases of infestation with the *Filaria bancrofti*, the lymphatics below become distended and tortuous, and a common result is rupture of some of the lacteals of the bowel or mesentery, with escape of chyle into the peritoneal cavity. There thus results what is known as *chylous ascites*, in which the fluid has a milky appearance owing to the presence of minute fatty globules. Apart from this, lymphatic obstruction *per se* is rarely a cause of local œdema, as there are so many collateral vessels. Sometimes, however, there is an extensive multiple obstruction of the lymphatics, say in the groin, by the ova and embryos of the filaria, and then important results follow. There is a certain amount of œdema, but owing to accompanying inflammatory change there may be much increase of the fibrous tissue, and the skin becomes irregularly thickened and indurated, a variety of what is known as *elephantiasis* being thus produced (p. 325). Lymphatic obstruction by malignant growth may accentuate the effects of venous obstruction and thus increase the œdema. This is well seen when a growth in the axilla, secondary to cancer in the breast, involves both the veins and the lymphatics. But an œdema of ordinary type with pitting of the skin is rarely, if ever, produced by lymphatic obstruction alone.

Angio-neurotic Œdema. Œdema may result from nervous disturbance and may thus be placed in the class of trophic neuroses along with acute hyperæmia, vesicular formation, and other trophic disturbances of the skin. The œdema is usually of an acute and transitory character, occasionally of more chronic type. Localised œdema of the skin may occur in organic nervous disease of chronic nature, e.g. in locomotor ataxia and syringomyelia, and it is met with also in hysterical conditions, sometimes associated with congestion of the part. Again, œdema may occur in severe cases of herpes zoster or shingles (p. 771) and is apparently a trophic effect due to inflammatory change in the posterior root ganglia. If the nerve lesion is unilateral, as is usually the case, the œdema stops short in the middle line of the body. A variety known as Quincke's disease often affects several members of the same family and is distinctly hereditary. In this condition the œdema occurs usually in the face or hands but may affect the larynx, and death in some cases has occurred from œdema glottidis. Œdema of the wall of the bowel attended by colicky pain has also been described. It is generally assumed that the trophic disturbance is one of the vessel walls, but a direct action on the tissues cannot be excluded; in fact, it is quite likely that the capillary endothelium and the tissues are affected together. The group of œdemas ascribed to nervous disturbances is, however, somewhat ill-defined, and some of them may be really of toxic origin and allied to urticaria.

Œdema of the Lungs. As has been stated, in this condition the fluid accumulates in the air vesicles of the lungs, and gradually replaces the contained air. A certain amount of œdema is common in the posterior parts of the lungs in death from various causes, but sometimes the œdema is of great degree and owing to the fluid a large proportion of the pulmonary tissue is airless or 'water-logged.' Welch showed that pulmonary œdema can be rapidly produced in healthy dogs by compressing the left auricle or ventricle, or by ligaturing the aorta, the result in these conditions being that the blood flow from the lungs is interfered with. Apparently a similar condition might result from a relative inefficiency of the left ventricle as compared with the right, and it is quite likely that pulmonary œdema is sometimes thus produced in the human subject, especially in cardiac cases. A recent view put forward is that a neurogenic factor is concerned in pulmonary œdema, but the nature of this factor is obscure. Pulmonary œdema of extreme degree is common in cases of nephritis with general œdema, though it is noteworthy that it often appears somewhat suddenly and increases rapidly, as if it were produced by some factor additional to that which causes the general œdema. It is to be noted too that pulmonary œdema is often of inflammatory origin; it is common, for example, in influenzal infections and as the result of the inhalation of irritating vapours. It may be caused also by fat embolism of the pulmonary capillaries. When œdema of the lungs is present for some time, organisms may gain a foothold, flourish in the fluid and set up inflammatory change, resulting in a type of pneumonia ; this is common when a state of coma has preceded death.

Pathology of Œdema

As it is now generally accepted that the processes of interchange of fluid between the capillaries and the tissue spaces can be explained on a physical basis, and that they do not involve secretion by the vascular endothelium as a factor, we shall discuss the question in accordance with this view. The distribution of fluid within and outside the capillaries is believed to be regulated mainly by a balance of the two processes of filtration and osmosis. The intra-capillary pressure tends to lead to the passage of fluid outwards into the tissue spaces, while the osmotic pressure of the colloids of the blood plasma tends to attract water and thus to induce its passage from the tissue spaces into the capillaries. Any disturbance of the normal balance of the two conditions will lead to the passage of fluid in one or other direction, as the case may be.

The capillary endothelium generally is said to be relatively impermeable to the proteins of the plasma, though the degree of permeability varies in different regions ; thus the hepatic capillaries have a considerable permeability. Impermeability when present normally may, however, be lost under conditions which can hardly be regarded as pathological ; for example, when the capillaries become dilated and their walls stretched (Krogh). Thus when there is a local venous congestion, not only is there an increased filtration of water with crystalloids owing to the heightened capillary pressure, but also a passage through the capillary wall of a certain amount of protein. It must be noted, however, that such increased transudation may occur without sufficient accumulation resulting in the tissue spaces to cause œdema. Again, damage of various kinds leads to increased permeability of the capillary wall with escape of protein-containing fluid in varying concentration. The extreme example of this is the inflammatory exudation, but all degrees of concentration are met with down to transudates with relatively low protein content. Histamine is a well-known example of a substance which causes a leakiness of the capillaries with escape of the blood proteins in large amount (p. 56). Another factor which may be concerned in the process of transudation is one resident in the tissues themselves, namely an increase of metabolites in the tissue fluids leading to increased osmotic pressure and thus to passage of fluid from the capillaries. This factor is seen in the acute œdemas resulting from traumatism, burns and in other examples of inflammatory œdema including toxic œdemas. It is often accompanied, however, by increased permeability of the capillaries. Any increase of molecules in the tissue fluids, however, will have only a temporary effect unless their supply is maintained ; since crystalloids diffuse freely through the capillary walls and the concentration without and inside the capillaries will soon become equalised.

Having given this general survey, we shall now consider the forms of œdema in more detail. It may be stated, however, that in many cases several factors are concerned and that various points with regard to the pathology of œdema are still unsettled.

Cardiac Œdema. With this may be included the local œdema resulting from venous congestion, and the more comprehensive term of *congestive* dropsy or œdema may be used. The close relation between venous engorgement and œdema, as observed clinically, has already been referred to. It has been established, however, by experiment, that in a healthy animal, ligature of a large venous trunk usually does not lead to œdema. As a result of the increased capillary pressure there occurs an increased formation of lymph of lower specific gravity than the normal, but this is got rid of by an increased flow along the lymphatics, and œdema does not result. If, however, along with the ligation of the vein the vasomotor nerves supplying the part be cut, the intra-capillary pressure is still further increased and œdema follows, as the increased transudate cannot be carried off. The application of an elastic band to a limb may merely produce venous congestion with increased lymph flow, but if the band be tightened to a degree sufficient to prevent the flow of lymph from the part, then œdema will result. Further, Wooldridge made the interesting observation that if a solution of tissue fibrinogen is injected into the circulation of an animal in which a vein has been ligatured, œdema occurs in the corresponding part. This result is of great importance, as it is difficult to see how the tissue fibrinogen can influence the result except by an action on the capillary endothelium.

Other examples might be given, but one may say that in experimental work on healthy animals, some other factor in addition to venous congestion is usually necessary for the production of œdema. It is to be noted, however, that in clinical cases of local venous congestion, the condition often lasts much longer than in experimental work. In cardiac cases too, general venous congestion may exist for a long time without œdema occurring. Increased transudation occurs from the congested capillaries as a result of their dilated state, as has been explained (there may be no increased capillary pressure); but for a time the body mechanism is sufficient for the prevention of accumulation of the fluid in the tissue spaces. Later, however, œdema may appear. These facts suggest that the diminished oxidation may in time affect the capillary endothelium and alter its permeability; this is probably a very important factor in congestive œdema. Further, it is likely that there is a certain accumulation of waste products in the tissues, which by their osmotic action will attract more water from the blood. And it is to be noted that in œdema generally, the distension of the tissue spaces with fluid will lead to a diminution in their physical resisting power and their elasticity. The power of passing on the fluid along the lymphatics is thus impaired, and a sort of vicious circle is established. In cardiac œdema there may be some diminution of the blood proteins with corresponding fall in their osmotic pressure, but this is much less marked than in chronic renal œdema. Another factor which must be of importance is the oliguria resulting from chronic venous congestion of the kidneys, especially when the heart is beginning to fail. We consider that the enormous amount of fluid in the œdematous tissues in some cardiac cases, as evidenced by the great increase of the body weight, is largely due to this factor. Furthermore, its importance is shown by the effects of diuretics in diminishing the œdema. These are some of the conditions which are concerned in the production of cardiac œdema, though it is not possible to say in what proportion each may be involved.

A theory of œdema which has led to much discussion is that of Fischer, according to which the œdema is due to an increased affinity of the colloids of the tissues for water. This increased affinity or hydrophilic character is brought about especially by accumulation of acids, which combine with the proteins and lead to their swelling in the presence of water. Fischer holds that there is abnormal production or accumulation of acids whenever the tissues suffer from anoxæmia, and also in other conditions in which œdema occurs. The theory, which has been the subject of considerable criticism, would appear to us to explain the swelling of the cells and fibres, which Fischer regards as the first change in œdema, but not the large accumulations of protein-containing fluid, which occur in the tissue spaces and serous sacs. In view of all the facts, the possibility of its application to the pathology of œdema in general seems to be rather limited.

Renal Œdema. It is now recognised that there are two types of this condition, one occurring rapidly at an early stage in acute glomerulonephritis and one occurring in certain cases of subacute nephritis and in the condition known as nephrosis. In the latter type which we may conveniently speak of as *chronic renal œdema*, the œdema reaches its highest degree and is often long-lasting, though remissions occur. The main factor in its production is now generally regarded to be a fall of blood protein leading to a fall in the colloid osmotic pressure. Albuminuria is a prominent feature and may be extreme, 15 grms. of protein per day being sometimes lost over a considerable period. The ratio of albumin to globulin in the urine is much higher than that in the blood ; in other words, there is a greater loss of albumin than of globulin. The result of such loss of protein continued over a time is a fall in the protein content of the blood, and this fall affects the albumin more than the globulin. The latter point is of importance, as albumin in solution has a considerably greater osmotic pressure than globulin (three to four times) owing to its molecules being smaller and thus, for a given weight, more numerous. Many observations show that these changes—the fall in protein content and the fall in the albumin-globulin ratio—are characteristic of chronic renal œdema, and direct osmometric measurements have shown a corresponding fall in the osmotic pressure of the blood. In accordance with the principle already discussed, the filtration pressure having less osmotic pressure acting against it, leads to the passage of water and salts through the capillary walls, and thus œdema results. This is in accordance with the low specific gravity of the transudate in this type of œdema, this being often below 1,005. There is no evidence that there is any increased permeability of capillary walls concerned; in fact, the filtrate leading to the œdema is little more than a saline solution. We must conclude that fall in the proteins of the blood plasma plays an important part in this form of renal œdema; whether it will account for all the facts remains to be seen. Kylin, for instance, holds that it is not the whole explanation as the œdema may diminish considerably without a corresponding rise of the colloid osmotic pressure of the blood, a fact difficult to explain.

The subject is a difficult one and it does not seem possible to ascribe chronic renal œdema to one causal factor. Along with the œdema which is general and often progressive oliguria is usually present in varying degree. Theoretically the diminished excretion of water by the kidneys might in itself lead to accumulation of water in the body and, the blood volume being kept constant, to its passage into the tissues. And, as will afterwards be described, certain kidney lesions do lead to varying degrees of oliguria. This view has been strongly and ably supported by Shaw Dunn. On the other hand, the oliguria might be the result of the escape of fluid into the tissues owing to the diminished colloid osmotic pressure of the blood, which is chiefly due to the loss of protein in the urine. Both these factors are no doubt concerned, but if our views with regard to the interchange of fluid through the capillary walls is correct, the latter cannot fail to be of important influence.

The view stated wth regard to chronic renal œdema is supported by the results of experimental production of diminished protein content of the blood by abnormal diets or by other methods. Such a condition, for example, has been produced by repeated bleedings of dogs over a long period of time, the red corpuscles being separated from the plasma after each bleeding, suspended in saline and introduced again into the circulation. When this procedure is continued over some weeks so marked a reduction in the blood proteins results that œdema appears. It may be noted, however, that the animals in question received a large amount of normal saline by the mouth, a point which may be of importance. The famine œdema above referred to (p. 45), also probably depends on a fall in the blood proteins.

The œdema of acute nephritis, *acute renal œdema*, presents certain differences from that of chronic renal œdema. It is of less severity and is less persistent, there is no fall in the blood proteins to account for it, and the specific gravity of the transudate is much higher, the amount of protein being sometimes several times that in the chronic type. The last fact suggests that the capillary walls have become more permeable, that is, partially permeable to proteins, and it is thus possible that the toxins which lead to the damage of the glomerular capillaries, which is the first event in this type of nephritis, act also on the capillary walls generally and bring about the increasing permeability. This view has received support from a good many writers on the subject. The relatively high specific gravity of the transudate may, however, be partly due to the fact that the œdema is of less degree than in other forms—i.e. a smaller proportion of water has been added to the tissue fluid. A further suggestion has been made, namely that the action on the capillaries is of allergic nature (p. 195), but this is largely speculative. As in the case of chronic renal œdema there is, however, another factor which must play a part, namely, retention of water in the body as the result of failure on the part of kidneys to excrete it. Both these factors may be concerned but until more definite knowledge as to capillary damage is obtained it is not possible to state their relative importance.

A few years ago the theory of *salt retention* was by many believed to explain the phenomena of the two types of renal œdema met with. It was believed that there was failure on the part of the kidney to excrete salt, especially sodium chloride, and that the retention of salt led to retention of water so as to maintain the normal isotonic state of the blood and tissue fluids. Increase of fluid thus resulted and as the blood volume was kept relatively constant the excess was passed into the tissues, œdema being produced. The facts on which this view was based are chiefly these. In cases of acute and chronic renal œdema oliguria is often associated with diminished excretion of chlorides and in the former there may be practically complete retention. This was repeatedly observed, for instance, in cases of war nephritis (p. 654). The œdema, however, is not invariably related to such retention and it has been shown that the kidneys may still have the power of secreting chlorides when œdema is present ; there may thus be some other explanation of the salt retention when it occurs. It has been suggested, for example, that the chlorides are simply deviated into the tissue fluids and do not raise the chloride content of the blood sufficiently to lead to their excretion by the kidneys. When diuresis occurs and the œdema is disappearing, chlorides are often in excess in the urine. Another striking fact bearing on the matter is that when a patient is fed on a salt-free diet, diuresis often follows and the œdema diminishes or disappears. The question is still one requiring explanation on many points, but it concerns not the retention of salt as such but of saline solution and is thus intimately bound up with the question of water retention.

VARIATIONS IN BLOOD VOLUME

When the volume of the blood is artificially decreased or increased, we find mechanisms coming into play which tend to restore the original volume. In the case of a hæmorrhage or artificial bleeding, if not too extensive, the arterial pressure, after falling somewhat, is restored nearly up to normal by contraction of the arterioles ; this may be regarded as a provision whereby a sufficient arterial blood supply to the brain and heart may be maintained. The contraction of the arterioles leads to diminished flow through the capillaries, and lowered pressure in them. As the colloid osmotic pressure is thus less opposed, absorption of fluid from the tissues occurs and the blood volume is gradually restored. The rapidity with which this takes place varies in different animals and according to the state of the tissues. It occurs with rapidity in rabbits, so that by the time an experimental bleeding has been performed, a considerable addition of fluid has been made to the blood, and as a result of the dilution there is a fall in the number of red corpuscles per c.mm. In the dog the process is more gradual, and after the removal of a considerable amount of blood, say about a quarter, the dilution of the blood is usually not completed for about twenty-four hours. In the case of the human subject absorption of fluid from the tissues takes place pretty rapidly. For example, it has been found that the removal of 800 c.c. of blood from a healthy man for purposes of transfusion, may be followed by a restoration of the ordinary blood volume in an hour (Keith). And certainly within a few hours after a large traumatic hæmorrhage the blood may appear distinctly watery.

It is to be noted that a rapidly fatal result from large hæmorrhage is produced, not by a loss of the corpuscles, but by the diminution in the volume of the blood, that is by a loss of circulating fluid ; probably the loss of about half the amount of blood will be fatal, but this will vary according to circumstances. To maintain the circulation a certain blood pressure is necessary. When the volume is diminished, less blood reaches the heart, and the pressure can be maintained only by contraction of the arterioles. This means slower flow in the capillaries, and ultimately too little blood reaches the heart for the maintenance of the circulation. The importance of restoring the fluid part of the blood is thus evident. Saline fluid, injected intravenously, is of some service, but only temporarily, as it is rapidly passed out of the blood into the tissues and also excreted in the urine ; it appears to be more efficient when injected into loose subcutaneous tissue. The restoration of fluid to the blood is aided by the administration of fluid by the mouth or rectum. The most efficient method, however, is transfusion of blood, and in carrying it out care should be taken that the serum of the patient does not agglutinate the corpuscles of the blood injected (p. 58). For cases where blood is not available, Bayliss introduced a colloidal solution with the same osmotic pressure as that of the blood. This consists of a 6 per cent. solution of gum arabic in normal saline solution. Recently, however, it has been largely replaced by citrated plasma. When hæmorrhage is complicated by the co-existence of shock (p. 55), however, all these methods may fail owing to a condition of increased permeability of capillary walls, as a result of which colloid-containing fluid continues to escape into the tissues and the blood volume cannot be restored and maintained.

The opposite condition, increase of the blood volume or *plethora*, may be artificially produced by the injection of fluids into the circulation, such as saline solution, blood serum, whole blood, etc., but the increase is only temporary. The increased volume thus produced leads in the first place to a slight rise in arterial blood pressure, and then to a vasomotor response, whereby there is a dilatation of the arterioles, with increased rate of blood flow and increased pressure within the capillaries. More blood reaches in a given time the right side of the heart, and its contractions become more powerful and frequent. There is thus established a more rapid circulation of the blood. The increased pressure within the capillaries leads to more rapid filtration through their walls, and there is also increased excretion of water by the kidneys. In these ways the increased volume gradually returns to normal—with comparative rapidity in the case of saline, more gradually in the case of fluids containing colloids, such as blood serum. When the blood volume of an animal is increased by transfusion of blood, the loss of fluid which follows is shown by increase of the number of red corpuscles per c.mm., and this condition of polycythæmia lasts for some time.

Apart from experimental conditions, the blood volume can be reduced by loss of fluid in various conditions, for example by excessive sweating, or by watery diarrhœa ; and the most striking example of the latter is seen in cholera, where the reduction may be very marked, the blood becoming inspissated, as it were, and there being a corresponding marked increase in the number of red corpuscles per c.mm. Diminution in blood volume may occur when there is an extensive escape of fluid into the tissues as a result of severe traumatism or burns. Another example is in the case of poisoning with irritant gases such as chlorine or phosgene in which there results a massive pulmonary œdema. In acute intestinal obstruction too the blood volume becomes reduced as part of the general dehydration of the body (p. 570). In all these conditions the blood volume becomes restored to normal when the cause is removed.

While in normal conditions artificial variations in the blood volume are soon got rid of by the mechanism described, in certain abnormal states the blood volume may be altered over a considerable period of time ; that is, *chronic variations* may be met with. Such variations are chiefly in the direction of increase, and in some the change may be regarded in the light of adaptation, but in others the cause is obscure. Lorrain Smith showed that the blood volume in chlorosis was increased sometimes to double the normal, and that this increase diminished as cure takes place. In this instance the explanation of the abnormality is not known. In splenomegalic polycythæmia, where there is an increased number of red corpuscles per c.mm., Boycott found in some cases that the blood volume was increased, that is, a true plethora was present. As he pointed out, this is probably the result of an adaptation by which the blood is diluted, and thus the frictional resistance resulting from the increased viscosity is lessened to a certain degree. In secondary shock there occurs a diminution of blood volume, as will presently be described.

SHOCK

Shock is a condition of profound depression of the various functions of the body. It may be caused by a variety of conditions—by severe pain such as in biliary colic, by various injuries, especially those of a crushing or lacerating nature, by certain abdominal lesions, e.g. perforation of the bowel, and occasionally by painful mental impressions and by operation procedures, especially when anæsthesia is not sufficiently deep. In a state of shock the skin is pale and covered with cold perspiration. The face is pinched and the eyes sunken ; consciousness is present, but there is usually a condition of restlessness or of torpor. The pulse is rapid, small and feeble, and the blood pressure is markedly diminished ; the peripheral blood vessels contain little blood and there is a lessened amount of bleeding from a wound. The respiration is weak and shallow and may be irregular, and the excretion of urine also is diminished. There is thus a condition in which disturbances of the circulatory and the nervous systems seem to be specially concerned. Important work, both clinical and experimental, was done on the pathology of shock during the late war, and two varieties, viz. *primary* and *secondary*, came to be distinguished. The former occurs immediately on receipt of injury or shortly thereafter, and appears to be chiefly of nervous origin. The latter occurs some time later and has a more complex pathology.

With regard to *primary shock*, there is evidence that a closely similar condition may be produced reflexly. Goltz showed that when a frog was suspended in an upright position, a sharp blow on the exposed mesentery produced a reflex dilatation of the abdominal vessels and inhibition of the heart, along with a marked fall in blood pressure. And it is well known that the stimulation of the central end of a sensory nerve may cause a similar fall. The view thus became current that in shock there is a great accumulation of blood in the splanchnic area and, owing to low arterial pressure, a diminished return of blood to the heart, with deficiency of the diastolic filling of the right ventricle. Whilst the above is probably the correct explanation of primary shock, it has been established that in secondary shock the most important factors are of a different kind.

Secondary shock, which may develop some hours after the injury, was of common occurrence during the war (1914–18) ; it was often complicated and intensified by hæmorrhage, though the essential features were met with in the absence of the latter. The symptoms tended to be aggravated by exposure to cold or by a general anæsthetic, such as chloroform or ether. It was found that, along with a fall in the blood pressure and in the temperature, there is a distinct diminution in the volume of the blood, and that this occurs, though not to the same degree, even where there has been no hæmorrhage. It was further established that in such cases the blood in the capillaries may be more concentrated, as indicated by the number of red corpuscles per c.mm., than that in the veins. When the condition is of severe nature, injection of saline does little good, as the fluid passes quickly from the capillaries into the tissues. Further, no evidence was obtained that in this condition there is an accumulation of blood in the abdominal veins. The explanation arrived at is, that during secondary shock there occurs a loss of tone in the capillaries, especially in internal parts, and the blood stagnates in them ; and that as there is a contraction of arterioles to maintain as far as possible the blood pressure, diminished circulation results. The amount of blood reaching the heart thus becomes seriously in defect. There may then develop an increased permeability or leakiness of the capillary wall, and an increased amount of fluid with colloids passes into the tissues ; hence the blood volume is diminished. When this stage has become well established it may be impossible to restore the blood volume even by defibrinated blood, as the colloidal solution so readily escapes into the tissues. The question thus came to be one as to the cause of the alteration in the capillaries and blood volume.

Dale and his co-workers showed that certain of the characteristic features of secondary shock can be produced in the cat by the injection of histamine in suitable doses. Histamine has a stimulating effect on plain muscle and this leads to contraction of arteries, but nevertheless, fall of blood pressure follows its injection, and ultimately there is a shock-like failure of the circulation. The cause of the latter is the action of histamine on the capillaries ; it leads to a loss of their normal tone, they become dilated and the blood stagnates in them, and at the same time their walls become very permeable and there is a loss of blood plasma. Thus, just as in secondary shock, the blood volume falls and the blood becomes more concentrated. It is interesting to note that the effects of histamine are intensified both by anæsthesia and by the previous withdrawal of blood.

From these results it appeared that secondary shock was of the nature of a toxæmia and this view gained general acceptance. It has now, however, been adversely criticised. One may state that histamine is not the substance concerned. It is scanty in muscle and histamine shock differs in its rapidity of onset from secondary shock, also in the state of the abdominal vessels. So far no depressor substances have been demonstrated in the blood coming from a traumatised limb. The view has been put forward that local escape of fluid into the damaged tissues is the primary factor in reducing the blood volume and that thereafter there are other contributory factors, the increased permeability of capillaries being ascribed to anoxæmia. This view has recently received considerable support. Again, it is held by others that an important factor is the continued transference of nervous impulses from the traumatised area. It is evident from what has been said that diminution of blood volume and an abnormal permeability of the capillaries leading to continued loss of fluid from the blood so that transfusion may be without effect, are the most important phenomena in secondary shock. It is, however, not possible to say to what extent the various factors—local loss of fluid from the blood, toxæmia, and a nervous element—are concerned.

Burns.[1] The pathology of burns is in certain respects closely related to that of shock. In burns too the factors of nervous disturbance, loss of fluid from the blood and toxæmia are involved. At a later stage there is also the factor of local bacterial infection and sometimes septicæmia. A feature of burns is the extensive area of tissue involved in proportion to actual mass ; and this area is a very vascular one. The effects of burning are of all grades of intensity from acute congestion and inflammatory œdema to actual charring of the tissues ; surgeons accordingly describe burns as being of different ‘ degrees ’ of intensity. It is generally recognised that the extent of skin affected is of importance at least equal to the degree of the lesion and also that the effects are more serious in children than in adults. A stage of *primary shock* occurring almost immediately after the burn is usually present ; this is mainly of nervous origin and death rarely takes place at this period. It is noteworthy, however, that a marked leucocytosis is usually present. The next stage is that of *secondary shock* which develops some hours later and is associated with a fall in blood pressure and with a diminution in blood volume and a heightened corpuscular count. There is also evidence of chloride retention. These features are evidently the result of the changes in the damaged area ; many small vessels and capillaries are thrombosed but others are damaged in less degree and there occurs an extensive exudation from them, resulting in inflammatory œdema. In this way the blood loses volume and the amount lost will vary with the area of the burn. Death not infrequently occurs during secondary shock about twenty-four hours after the injury though it may be later, but it is much commoner during the next stage, viz. that of *acute toxæmia*.

In *acute toxæmia* the symptoms are different from those during shock and appear about the second day. The temperature rises, sometimes markedly, and the blood pressure may be for a time normal ; pulse and respirations are quickened, vomiting is common and sometimes the vomit contains altered blood. The circulation gradually fails ; the patient becomes drowsy or delirious and ultimately comatose before death. These symptoms of toxæmia are most severe in extensive superficial burns. About two-thirds of the deaths following burns occur in this stage, usually about two or three days after the burn. Such symptoms must be due to different causes from those of shock. Wilson has found that there may be no evidence of blood concentration and that there are not sufficient chemical changes in the blood to account for them; nor is there any evidence that bacterial growth is concerned. It is generally believed that the essential factor is the absorption of toxic substances resulting from the autolysis of tissue proteins in the damaged area, and for this view there is experimental evidence. In particular, Wilson and his colleagues found that in experimentally produced burns the tissue fluid had distinctly toxic properties, these being slight at first and afterwards increasing. Injection of such fluid produced death in animals with evidences of toxic damage in organs, especially in the liver. There is thus strong evidence of toxic action in this stage. The method of treatment of burns by tannic acid has led to a marked fall in the mortality. In acute toxæmia it is believed to act by producing a coagulation of proteins and thus preventing exudation into the tissues and autolytic breakdown.

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[1] For details see *The Tannic Acid Treatment of Burns*, by W. C. Wilson. Rep. Medical Research Council, London, 1929.

A fourth stage recognised is that of *bacterial multiplication* with toxic absorption of bacterial products and occasionally septicæmia. During this there occurs a growth of organisms in the damaged area and this will be specially the case when the tissues contain much fluid. It is apt to be of serous nature especially when the effects of the burn have been deep. A number of organisms are concerned but the most serious effects are those produced by the *Streptococcus hæmolyticus*. The use of tannic acid is beneficial during this period by leading to a drier condition of the tissues, bacterial growth being less in consequence.

The post-mortem changes, which are not characteristic, are most marked when death has occurred somewhat late. They are chiefly cloudy swelling with congestion and sometimes small hæmorrhages in organs; the last-mentioned are sometimes marked in the adrenals. Focal necroses may be found in the liver and adrenals, notably in the former where they may be a marked feature. Acute ulceration of the duodenum is sometimes present but it is rare; it occurs especially when life has been prolonged. Its causation has been the subject of much dispute but nothing definite has been established.

In cases where recovery takes place the usual processes of healing follow. When the burn has been deep the fibrous tissue formed may be abundant and lead to cicatricial contraction and deformity.

Iso-agglutination in Relation to Transfusion. The blood serum of one individual may have the property of producing agglutination or hæmolysis of the red corpuscles of another, and in carrying out transfusion it is essential to use corpuscles which are not acted on in these ways by the serum of the recipient. As hæmolysis does not occur without agglutination, it is sufficient to test only for the latter; this can be readily carried out as follows. A few drops of the blood of the prospective donor, that is the blood to be tested as regards suitability for transfusion, are allowed to fall into 1·5 per cent. solution of sodium citrate in normal saline solution, in a small test tube; the tube is then shaken so as to produce a uniform suspension. A small amount of blood likewise is taken in a small pipette from the patient to be transfused, and after clotting has occurred the serum may be obtained by the centrifuge or simply allowed to separate out. A drop of the suspension of red corpuscles is put on a glass slide, a drop of the patient's serum is then added, and a mixture is made. If an iso-agglutinin is present in the patient's serum the mixture rapidly loses its uniform appearance and minute granular masses are seen. If such agglutination takes place the particular blood in question is not suitable for transfusion into the patient.

It has been found that the corpuscles and sera of different individuals can be classified into four groups, which interact as shown in the following table drawn up by Moss :—

	Red Corpuscles of Group			
Serum of Group.	*I* (AB)	*II* (A)	*III* (B)	*IV* (O)
I	0	0	0	0
II	+	0	+	0
III	+	+	0	0
IV	+	+	+	0

+ = agglutination. 0 = no agglutination.

For explanation of letters (AB), etc., see paragraph below.

It will be seen that the serum of Group I agglutinates the corpuscles of no group : an individual of Group I can thus receive the corpuscles of any other group, and is thus a "universal recipient." The corpuscles of an individual of Group IV are agglutinated by the serum of no group ; his corpuscles thus can be used for transfusion into an individual of any group, that is, he is a "universal donor." It will be seen also that if one has known sera of Groups II and III, one can determine the group to which the corpuscles of any individual belong. If the corpuscles are agglutinated by both sera, the blood belongs to Group I ; if agglutinated by serum III only, it belongs to Group II ; if agglutinated by serum II only, it belongs to Group III ; if agglutinated by neither serum, it belongs to Group IV.

The results have been explained by Landsteiner as due to the presence or absence of two agglutinable groups or receptors (A and B) in the red corpuscles of different persons, and also to the invariable absence from each individual's serum of those agglutinins corresponding to the receptors contained in his own red cells. Thus the red cells of Moss's groups would contain the receptors as shown in the Table, the corpuscles of Group I containing both receptors A and B, and those of Group IV being devoid of both.

CHAPTER II

INFLAMMATION [1]

Introductory. The conception of inflammation as an important process in disease has come down to us from early times, and has had a dominant influence both in surgery and in medicine. Celsus gave as its cardinal signs, *tumor*, *dolor*, *rubor* and *calor*, and even to the popular mind an inflamed part is a red, hot and painful swelling. To these signs, Galen added another of importance, namely *functio læsa*, or impaired function. When cellular pathology was established on a scientific basis the phenomena of inflammation naturally came to be investigated and analysed by precise methods, and an explanation sought for. Virchow observed the increased cellularity of an inflamed part, though he considered the cells to be formed locally, and regarded the process as a disturbance of nutrition, owing to which the cells of the part required additional nourishment, which was supplied by the exudate It is to Cohnheim, however, that we owe the first full description of the phenomena of inflammation as studied under experimental conditions. He emphasised the important part played by damage to the vascular endothelium in bringing about the changes, and described in detail the process of exudation and the emigration of leucocytes. The results obtained by Cohnheim were confirmed in the main by those of other observers. One must bear in mind that at that time chemical irritants chiefly were employed in the production of inflammation and nothing of exact nature was known as to the causes of inflammation under natural conditions; and one can imagine how mysterious its onset and course must have appeared.

A new era commenced, however, when, after the discovery of bacteria as causes of inflammation, Metchnikoff studied the behaviour of the cells in the presence of bacteria, and established the importance of *phagocytosis* in the destruction of the latter. His work was part of a general enquiry into the manner in which cells throughout the animal kingdom defend the organism against micro-organisms or other harmful particles, and he arrived at the conclusion that, in animals with a vascular system, inflammation represents a means for the furtherance of phagocytic action; in other words, phagocytosis is the essence of inflammation. There has thus been a swing of the pendulum from the idea that inflammation is the result of damage to that of its being a defensive reaction. If, however, we are to retain the term according to the general conception, inflammation is not a single process, but a complex phenomenon involving several distinct processes, each of which is to be considered separately. It would be fruitless at this stage to attempt a definition, but we may use the short description of inflammation given by Burdon Sanderson as convenient and helpful. He regarded inflammation as " the succession of changes which occurs in a living tissue when it is injured, provided that the injury is not of such a nature as to at once destroy its structure and vitality." We shall see that the most important of these changes are of a defensive and beneficial nature, leading to the removal or destruction of the irritant, and preparing the way for repair of the injured tissues. But it does not appear justifiable to regard inflammation as a whole in this way, since to do so would be to exclude some vascular phenomena which are the direct result of damage.

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[1] For further details, reference may be made to Cohnheim's *Lectures on General Pathology* (New Sydenham Society), Metchnikoff's *Comparative Pathology of Inflammation* (translated by F. A. and E. H. Starling), London, 1893, and the most recent work, *Dynamics of Inflammation*, by Valy Menkin, New York, 1940.

Inflammation may be of varying intensity and duration, and it is often described as acute, subacute or chronic. We shall consider it under the two main headings of *acute* and *chronic*, but it must be understood that all intermediate stages are to be met with. Acute inflammation is characterised especially by vascular disturbances and exudation, and hence it is said to be of the *exudative* type. In the less acute and chronic types proliferation of the cells of the tissue and new formation of blood vessels are prominent features, and the inflammation is said to be of the *productive* or *formative* variety. An acute inflammation may subside and the condition of the part may return practically to normal, as is well seen in acute lobar pneumonia, or, on the other hand, it may pass into a subacute or chronic condition. Further, an acute inflammation may progress and be attended by softening of the tissues and the formation of pus, that is by *suppuration*. The latter, which will be conveniently described apart, is often spoken of as a sequel, but it is really a part or variety of inflammation caused by certain organisms. With this explanation, we shall first give an account of the phenomena of acute inflammation up to the point when there is no actual destruction of tissue, such as occurs in suppuration. We shall afterwards consider the results which may follow when this stage has been reached.

ACUTE INFLAMMATION

In describing the changes which occur in acute inflammation in a vascular part, we shall closely follow the accounts given by Cohnheim and Thoma. The phenomena are essentially the same in cold-blooded vertebrates and in mammals, though they occur more rapidly in the latter. The first marked effect of applying an irritant to a vascular membrane, such as the mesentery, is the production of an active hyperæmia, and this is to be regarded as merely a physiological response. The nervous mechanism and other factors have already been considered (p. 13). The vascular dilatation is sometimes preceded by a contraction which is, however, of short duration, often momentary. In active hyperæmia, the small arteries and capillaries become dilated, while the blood flow through them becomes accelerated. The capillaries appear to increase in number because many of them, formerly empty, become filled with blood. Although a certain amount of capillary dilatation results from dilatation of the arterioles, the capillaries have independent powers of contraction and dilatation, and they themselves actively respond. The mechanism concerned has been discussed in a previous chapter (p. 13). And there is also the fact that, when arterial hyperæmia is produced by section of the vaso-constrictor nerves, the application of an irritant causes still further capillary dilatation. It may be said that in the production of the capillary hyperæmia, an active dilatation of the capillaries probably plays a more important part than does the dilatation of the arterioles. At the same time, there is a slight escape of protein-containing fluid through the capillary walls. The part becomes redder to the naked eye, and is slightly swollen. The stage of active hyperæmia, however, is soon followed by a gradual slowing of the blood stream in the capillaries ; this goes on increasing in degree, although the capillaries remain dilated as before, or even undergo still further dilatation, and many become varicose. This process of stagnation may ultimately terminate in complete stoppage of the blood flow or stasis (p. 67), which may even be attended by coagulation of the blood, although this extreme result occurs only in intense inflammation. The slowing of the blood stream is accompanied by the important phenomena of *exudation*, *emigration of leucocytes*, and *escape of red corpuscles* ; these will now be described.

During the whole period of slowing of the blood stream, there occurs an exudation of lymph through the capillary walls in increasing amount. The exudate accumulates in the connective tissue spaces, and leads to further swelling of the part ; in many cases it undergoes coagulation and a reticulum of fibrin is formed, whilst in other instances the exudate remains fluid. Whether or not fibrin is formed depends in part on the nature of the irritant ; thus some organisms tend to produce a fibrinous exudate, others an abundant serous exudate. It depends also on the position of the inflammation ; thus a fibrinous exudate is specially common in the case of serous membranes, pericardium, peritoneum, meninges, etc., and it is usually a marked feature in the lungs in acute lobar pneumonia (Fig. 24). The process of coagulation with formation of fibrinous reticulum is, no doubt, due to the concentrated lymph coming in contact with the damaged tissues, which set free a thrombokinase. During the process of exudation, there is greatly increased flow of lymph in the lymphatics from the inflamed part, but this is not sufficient to prevent accumulation in the affected tissue. This lymph contains much more protein and has thus a higher specific gravity than normal lymph.

In normal conditions, the corpuscular elements of the blood form a central column in the blood stream, separated from the endothelium by a narrow zone of clear plasma in which a leucocyte may be seen from time to time. When the stream has slowed, the leucocytes fall out from the central part and accumulate in the peripheral zone of plasma in increasing numbers. This occurs especially in the smallest veins, though also in the capillaries, and in the former they may form an almost continual layer of cells, a condition which Cohnheim called 'pavementing' of the endothelium. Further, instead of rolling along as normally, many show signs of adhering to the endothelium, and present the appearance of being dragged along by the blood stream.

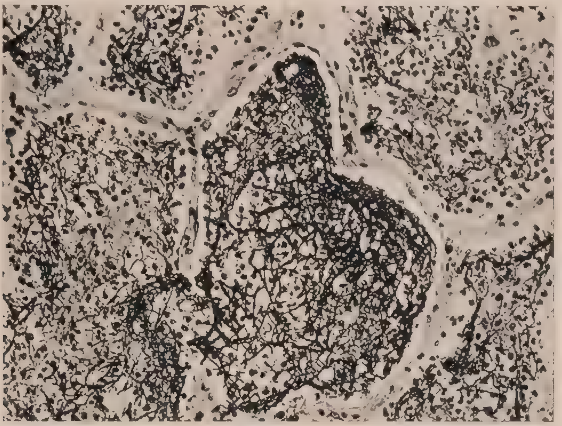

FIG. 24.—Acute Inflammation of Lung, showing Reticulum of Fibrin and numerous Polymorpho-nuclear Leucocytes (Weigert's fibrin stain). × 200.

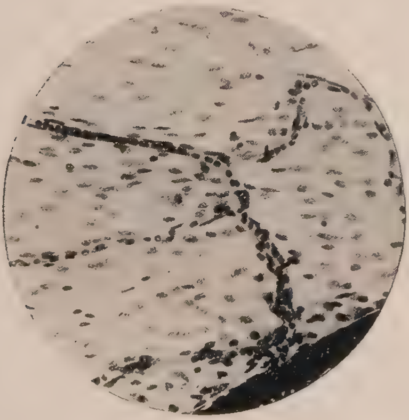

FIG. 25.—Surface View of Normal Omentum of Guinea-pig. (Prof. D. F. Cappell.) × 150.

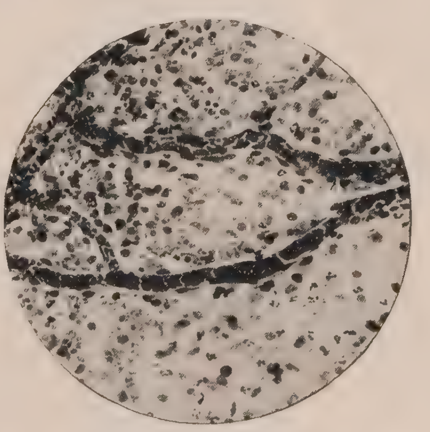

FIG 26.—Inflamed Omentum of Guinea-pig, showing Emigration of Leucocytes, increased Cellularity, and Engorgement of small Vessels. (D. F. C.) × 150.

The accumulation of leucocytes at the periphery has been shown to be merely a mechanical phenomenon, in which the relative specific gravity of the corpuscles is the chief factor; the leucocytes being lighter are driven from the central column of flow. There soon follows what is probably the most important phenomenon in inflammation, namely an emigration of leucocytes, which occurs through the walls both of the capillaries and of the small venules, especially

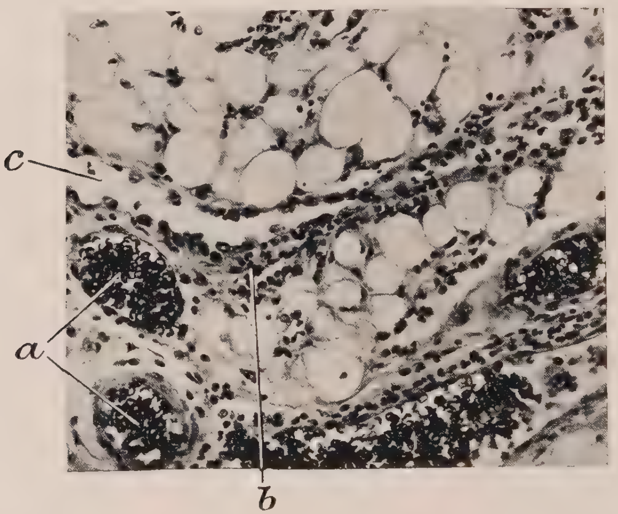

Fig. 27.—General View of Omentum in early stage of acute Inflammation showing (*a*) the intense Engorgement of Vessels, (*b*) Infiltration of Leucocytes around, (*c*) the Swelling of the Endothelial Cells. (G. H. W.) × 60.

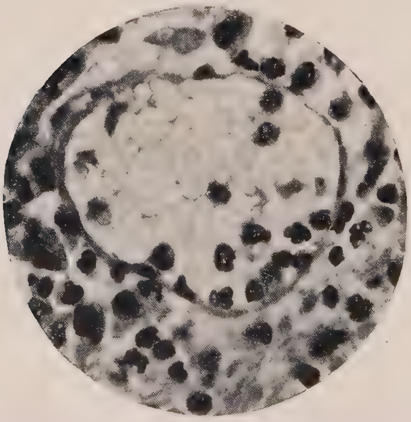

Fig. 28.—Section of small Venule in acute Inflammation, showing the Polymorpho-nuclear Leucocytes both inside and around the Vessel. (G. H. W.) × 600.

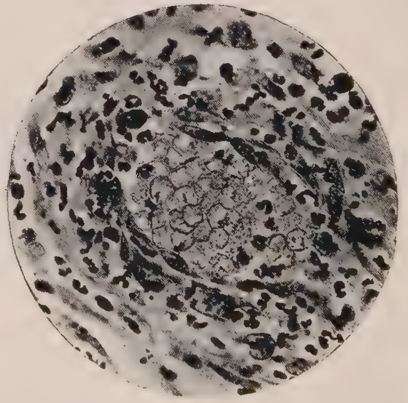

Fig. 29.—Inflammatory Change round small Vessel in Granulation Tissue.

Note the polymorpho-nuclear leucocytes emigrating through the wall. × 400.

the latter (Figs. 28, 29). The passage of the leucocytes through the vessel wall is a somewhat gradual process; a small portion of the protoplasm is extruded, and this gradually increases in amount until ultimately the whole cell has made its way through. It seems that the polymorphous character of the nucleus of the leucocytes which emigrate most rapidly may be regarded as a suitable adaptation for the passage of the cell through the minute aperture. The leucocytes, after emigrating, wander through the tissues in various directions, being guided especially by the presence of bacteria or other noxæ, as will afterwards be described. The result thus comes to be that the tissues around are overrun with large numbers of leucocytes (Figs. 26, 27).

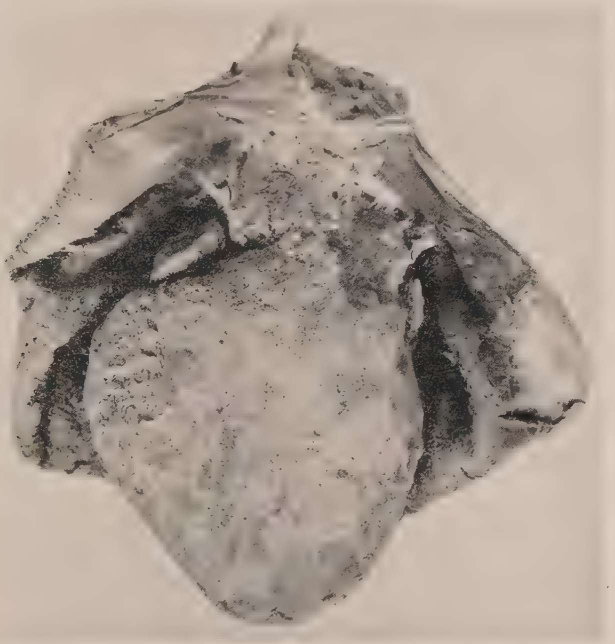

Fig. 30.—Acute Pericarditis, showing irregular Layer of reticulated Fibrin on the Surface of the Heart.

Along with these processes of exudation and emigration of leucocytes there is also an escape of red corpuscles, known as extravasation, into the tissues. This occurs, like the emigration of leucocytes, between the endothelial cells; and the corpuscles may escape singly, or sometimes in small jets especially where the capillaries are distended and varicose. The small aperture in the vessel wall immediately thereafter closes again, the breach of continuity being only momentary. Such a process is called *diapedesis*, as distinguished from hæmorrhage by *rhexis*, where there is a permanent rupture of the wall. Diapedesis of red corpuscles occurs in very varying degree, but it is always present, and the exudate as well as the lymph leaving by the lymphatics, shows a corresponding amount of blood-staining. In an acute pneumonia or pleurisy, red corpuscles are always to be found amongst the fibrinous reticulum. We may thus say that in an acute inflammation there is a passage into the tissues from the blood of (*a*) a fluid exudate which may or may not coagulate, (*b*) leucocytes, and (*c*) red corpuscles. We shall presently consider the significance of these various phenomena.

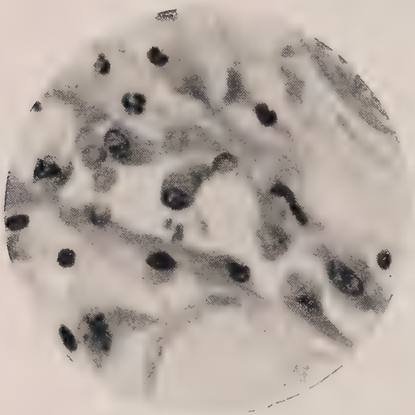

FIG. 31.—Lymphatic Channel of Omentum in acute Inflammation. The endothelial cells are becoming swollen and separated. (G. H. W.) × 600.

Whilst these vascular phenomena are occurring, the fixed cells in the inflamed part also show alteration. Endothelial cells, for example, those on a serous membrane, lose their flattened form, become enlarged and swollen, and ultimately free in the surrounding fluids (Figs. 27, 31). Swelling and proliferation of the endothelium of the capillary walls are seen at an early stage. Certain other cells belonging to the reticulo-endothelial system, histiocytes, etc. (p. 82), likewise become swollen and actively phagocytic, ingesting bacteria, other cells or red corpuscles. Fibrocytes increase in size, the cytoplasm becoming more abundant, and they also, in their turn, become separated from their fibres, and lie free in the lymph as fibroblasts; they become more prominent and numerous at a later period (Fig. 32). Within a short time both endothelial cells and fibroblasts may show signs of active division by mitosis, and thus still further increase the number of cells in the inflamed part. It is important to note that the specialised cells of an inflamed organ show various degrees of damage, up to actual necrosis (Fig. 33). This is, of course, a direct effect of the irritant or noxa, and is not a reactive phenomenon.

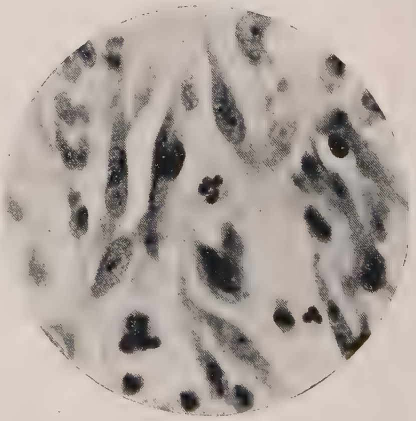

FIG. 32.—Fibroblasts, showing the characteristic appearance. (G. H. W.) × 600.

Having thus briefly sketched the main phenomena in the establishment of an acute inflammation in its earlier stages, we may now consider more in detail the nature and significance of the chief changes. It is unnecessary to refer further to the preliminary active hyperæmia, as this is really a physiological response (pp. 11–14).

(1) **Stagnation of the Blood and Diapedesis of Red Corpuscles.** The passage from the accelerated flow in ordinary arterial hyperæmia to the stage of stagnation is of prime importance. The appearance is as if increased frictional resistance were applied at the margin of the stream, and this is apparently due, as Cohnheim showed, to some damage to the endothelial cells which alters the character of their surface. In inflamed areas the endothelial cells of the capillary walls often are more prominent than normally, and this may be an indication of the important alteration in the frictional resistance. As the stagnation goes on, the blood also becomes somewhat thickened or inspissated, owing to its losing part of its plasma by exudation. There is thus produced an increased viscosity of the blood in the inflamed part, and this, along with the adhesive layer of leucocytes, may further interfere with the flow. Loss of fluid as a factor can readily be shown by applying concentrated salt solution to a vascular membrane, e.g. the mesentery of the frog. Stasis quickly supervenes owing to the rapid passage of fluid from the capillaries in response to the increased osmotic pressure outside. Alteration of the capillary endothelium must, however, be regarded as the prime and most important cause of the slowing. And Cohnheim found that by whatever means the vascular endothelium was damaged, all degrees of stagnation up to complete stasis followed, and that along with the slowing there occurred margination of the leucocytes and other phenomena as described above. Stagnation and stasis are also seen as the result of acute venous congestion, as in intestinal strangulation, fluid escaping from the engorged capillaries. They occur also at the margin of infarcts, at the junction of the living and dead tissues where there are all degrees of damage to the vascular endothelium as well as interference with the circulation. Stasis in such conditions is often attended by hæmorrhage. In very severe inflammations stasis may be followed by thrombosis and actual necrosis of the vascular endothelium.

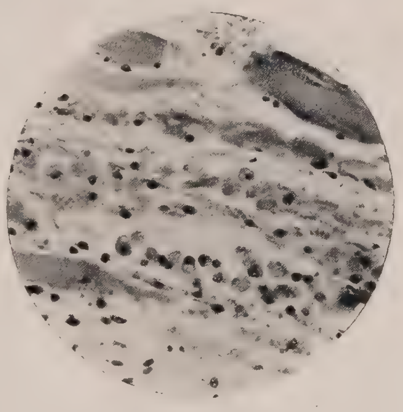

Fig. 33.—Acute Inflammation of Muscle, showing numerous Mononuclear Cells, some of which are derived from the Sarcolemma. The fibres are in process of disintegration and absorption. × 200.

All are agreed that the escape of red corpuscles in inflammation is purely a mechanical matter, the result partly of the pressure inside the capillaries and partly of the damage to the endothelium.

(2) **The Exudation.** With regard to the exudation there are two main questions to be considered. One question concerns the *mechanism* by which it is brought about, and the other its *effects*. In considering the first, it is manifest that our interpretation must depend on the process of normal lymph formation. If we adopt the filtration theory, there is in inflammation not only an increased flow to be considered but also an increased concentration of the lymph; and both of these would be readily explained by an increased permeability or porosity of the capillary endothelium, caused by damage. It would be an attractive view to suppose that the increased passage of concentrated lymph represents a reactive or defensive mechanism, but the facts do not seem to justify us in regarding the exudate in this light. It is also to be noted that, with the escape of red corpuscles, which is clearly a mechanical process, there must be a certain escape of plasma, which will add to the concentration of the exudate. The extreme result of damage is necrosis of the capillary wall and thrombosis within, and between that and the normal state there must be all degrees of damage and impairment of function; and it is in these intermediate stages that we see the phenomena of stagnation, exudation, and diapedesis of red corpuscles. In view of all the facts, it seems that the exudation is, as Cohnheim maintained, the result of damage to the capillary endothelium.

As we have said, the question as to the *effects* of the exudate is another matter. These are, on the whole, beneficial. The exudate is said to dilute the irritant, and if this is of purely chemical nature, the results will be favourable. On the other hand, if the irritant is of bacterial origin, as is usually the case, not only the bacteria, but also the leucocytes which deal with them, will be diluted. This is well recognised in surgery, and partly on this account precautions are taken, e.g. by drainage or posture, to prevent an accumulation of inflammatory exudate. The exudate when first formed may be regarded as possessing the various properties of the blood serum. In some instances it has a directly bactericidal action, but it must be recognised that the species of bacteria which are killed in this way form a comparatively limited group. Without actually killing the bacteria, however, the exudate may have an inhibitory action on their growth, and it has another very important effect in making them susceptible to phagocytosis by the leucocytes. It was shown by Wright and Douglas, by means of *in vitro* experiments, that the normal serum contains substances, called by them *opsonins*, which become united to and act on the bacteria, so that they are ingested by the leucocytes. They showed also that phagocytosis of bacteria does not take place in normal saline or in serum previously heated at 55° C., at which temperature the opsonins are destroyed. The various anti-bacterial substances in an exudate soon become used up in the presence of bacteria, and the exudate then becomes a favourable culture medium. Hence there is an advantage in promoting by efficient drainage or otherwise, a flow of fresh exudate from an infected cavity or wound. The treatment of infected wounds by hypertonic saline solutions depends on the same principle ; the increased flow of exudate from the blood vessels thus brought about acts not only mechanically by washing off the bacteria, but also by bringing with it an additional supply of anti-bacterial substances.

A fibrinous exudate not infrequently is of benefit in gluing the parts together, and preventing the spread of the bacteria. This is well seen in the case of appendicitis, where the coagulated lymph often localises the organisms, and accordingly the inflammation, to the region of the appendix, and prevents a general infection of the peritoneal cavity ; numerous similar examples might be given. On the other hand, the fibrous tissue which forms from organisation of the exudate may produce harmful results ; in the case of the peritoneum the resulting adhesions or bands may lead to obstruction or strangulation of the bowel. This is an example of what is almost a general law, namely, that any process usually beneficial may in certain conditions do harm.

(3) **Emigration of Leucocytes.** With regard to this, one may make the categorical statement that the leucocytes emigrate by their own amœboid movements, and are guided by substances in solution around them, that is, by chemotaxis. Certain chemical substances in solution attract leucocytes just as they do unicellular organisms, e.g. protozoa, bacteria, etc., and, in this case, the cells tend to move from a less to a greater concentration of the solution. A few substances act in a neutral manner, whilst others, again, are stated to repel the leucocytes, that is, exert a negative chemotaxis. The chemotactic effect of various substances can be conveniently tested by putting the substance as a solution or suspension in a capillary tube which is left open at one end, and then placing the tube in the peritoneal cavity of an animal. If the substance has a positive chemotactic effect, the leucocytes gather round the open extremity, and also make their way into the interior of the tube.

In accordance with what has been said as to chemotaxis, the amount of leucocyte emigration is not at all in proportion to the severity of the inflammation or in proportion to the amount of exudate ; the latter may be abundant, whilst leucocytes are comparatively scanty. This statement holds with regard both to chemical irritants and bacteria. Then again we find that different kinds of leucocytes emigrate in response to different bacteria or substances in solution —a fact which it would be quite impossible to explain if emigration occurred in a mechanical way, as was at one time supposed. Leucocytes, after emigrating, may take up bacteria in their neighbourhood, although the amount of phagocytosis varies in different cases. The ingested organisms may undergo digestion and destruction, or, on the other hand, the leucocytes may become degenerate or may be killed. In a few instances, the organisms appear to flourish well within the leucocytes, while the latter also appear to be uninjured. This is well seen in the case of gonorrhœal infection. Whilst inflammation may be produced by various chemical substances, progressive inflammation may be said to be due to micro-organisms. It may be arrested by their death within the cells, i.e. following on phagocytosis, or by their extra-cellular destruction. The polymorpho-nuclear leucocytes are also the source of certain anti-bacterial substances which become free in the serum, and the digestive enzymes which these cells contain become discharged in the surrounding medium. Thus in the neighbourhood of polymorpho-nuclear leucocytes we see fibrin and other substances being digested and disappearing apart from actual phagocytosis ; and the digestive softening of damaged tissue elements, which is so characteristic a feature in suppuration (p. 73), is also to be ascribed chiefly to the ferments produced by them.

If we regard as a whole the process of emigration of leucocytes and their subsequent behaviour, we must interpret the phenomena as representing a defensive mechanism ; and, as we shall see later, there is also a mechanism by which a practically unlimited supply of leucocytes from the blood to the tissues can be kept up. But while the leucocyte reaction is the most important phenomenon in inflammation and is protective in nature, we cannot regard inflammation entirely in this light. In the production of other essential phenomena—stasis, exudation, etc., injury to the vascular endothelium plays an important part. We are thus led to the conclusion that *inflammation is not a single process but a group of processes, which are essentially of different kinds.*

In view of what has been stated, it appears impossible to define inflammation as a pathological process. Difference of opinion may exist with regard to the nature and significance of vascular stagnation, exudation, and emigration of leucocytes, etc., but there is no doubt as to what these terms mean. With inflammation the case is different, and we have the unusual occurrence—almost unique in connection with a scientific subject—of discussion as to the pathological significance of inflammation when hardly any two writers are in agreement as to what the term means. In fact it seems to us that, were it not that the term came into use at an early period, it would never have emerged as the result of the scientific analysis of pathological processes. An indication of the difficulty is shown by the fact that Aschoff has recently proposed that different types of inflammation should be distinguished, viz. *defensive*, *reparative* and *regenerative* inflammation. Such an arrangement would seem, however, to deprive the term ‘ inflammation ’ of any distinctive character, in fact would make it synonymous with ‘ reaction,’ and it would not be practicable to bring it into harmony with clinical usage. There is also the more serious objection, namely, that in acute inflammation as ordinarily understood, there are involved changes such as stagnation of blood stream and probably also exudation which, as we have stated above, should not be regarded as of reactive nature. We consider that it would be better to use 'inflammation' as merely a convenient descriptive term, since it is not a distinct process capable of definition.

Varieties of Acute Inflammation. The above is an account of the changes seen in the establishment of acute inflammation, but the main features vary in different cases. *Varieties* of inflammation are accordingly often described, but these depend mainly on the prominence of one or more of the chief factors. As has been stated, when inflammation occurs in organs there is evidence of direct damage done to the specialised cells, varying in degree from cloudy swelling to actual necrosis, and the damage may be followed by reparative proliferation of the surviving cells. The term *parenchymatous* is sometimes applied when the specialised cells are much implicated in the inflammatory process, but there is little advantage in the use of the term. A *catarrhal inflammation* is one which affects a mucous membrane and is attended by increase of secretion and desquamation of epithelial cells; the term is used also in the case of acini and ducts of glands (p. 75). Variations depend too upon the character of the exudate, and different terms have accordingly come into use. Thus the exudate may be abundant and remain fluid, and the term *serous inflammation* or *inflammatory œdema* is then applied; it may be more concentrated and much fibrin may form—*croupous* or *fibrinous inflammation*; and there may be extensive extravasation of red corpuscles—*hæmorrhagic inflammation*, which is often accompanied by abundant exudate. The inflammation may be attended with much necrosis of tissues—*necrotic inflammation*. A distinction is sometimes made between *croupous* and *diphtheritic* or *pseudo-membranous*; the former is synonymous with fibrinous, in the latter there is formation of false membrane composed of necrosed epithelium and fibrin. The latter type of lesion is exemplified in the case of diphtheria of the fauces and in dysenteric lesions of the intestine. The term *suppurative inflammation* is applied when there is a digestive softening of the tissues with formation of pus; this will be described later. *Phlegmonous inflammation* is one in which there is much necrosis of tissues along with purulent infiltration.

Further Stages of Acute Inflammation. After the phenomena of acute inflammation have been established as above described, there may follow various results, of which the three following are the most important:—

(*a*) The inflammation may undergo resolution, and the part may return more or less completely to normal.

(*b*) It may progress and suppuration may follow.

(*c*) It may pass into a chronic phase, in which the phenomena are closely similar to those in the process of repair.

We shall now consider the two first of these results; the third will be dealt with in the next chapter in connection with chronic inflammation.

Resolution. In this process there occurs a retrogression of the various phenomena. The stagnation gradually passes off and the blood-flow is restored, though a certain amount of vascular dilatation often persists for some time; this is well seen when there has been an acute inflammation involving the skin. The exudate, if fluid, is absorbed chiefly by the lymphatics, and fibrin is digested by leucocytes and thereafter absorbed. If, however, the fibrin is abundant or dense, its absorption is effected only after the ingrowth of fibroblasts and capillaries, i.e. by a process of organisation (p. 113). This is the common result in the case of a fibrinous exudate on a serous membrane. Connective tissue cells, which have become swollen and separated in an inflamed part, diminish in size and become attached again to fibres, or form new fibres; and defects in endothelial linings may be completely restored by the surviving cells. It is quite likely that healthy leucocytes may pass back through the endothelium of the capillary walls to the blood stream; but those that are damaged, and also the extravasated red cells, are either taken up by phagocytes, or are carried by the lymph to the lymphatic glands, where they are similarly dealt with.

This process of what may be called cleaning up or scavenging, can often be well studied in the case of serous cavities. It is easy to produce in rabbits by intra-peritoneal injection of a suitable suspension of staphylococci, an inflammatory reaction which is rapidly recovered from. Within an hour or two after the injection, polymorpho-nuclear leucocytes in large numbers emigrate from the vessels and rapidly ingest the cocci. The emigration of these cells continues, until, in a favourable result, the organisms are destroyed. At a comparatively early date some non-granular cells also are present, and these at first can readily be identified as of two main kinds, viz. hyaline or mononuclear leucocytes, which have emigrated from the blood vessels, and cells of local origin, mainly of the histiocyte class (p. 81) which have become separated and globular in form. Later, such cells become somewhat altered in character, the hyaline leucocytes tending to increase in size, so that there is a group of non-granular cells or *macrophages*, and it may not be possible to distinguish the source of the individual cells. During the process of destruction of the cocci many of the polymorpho-nuclear leucocytes are seen to be in a degenerated condition, their nuclei being fragmented and changed into deeply staining chromatin globules.

There then follows an interesting phenomenon, namely the phagocytosis of these polymorpho-nuclear leucocytes by the non-granular cells or macrophages (Fig. 34). Both the hyaline leucocytes and the cells of local origin take part in this process, and within a macrophage there may sometimes be seen several polymorpho-nuclear leucocytes; the ingested leucocytes are gradually digested and disappear. Damaged red corpuscles also are taken up by these phagocytes and destroyed. Quite a similar phenomenon is to be seen in the sinuses of the lymphatic glands in relation to the site of inflammation, the damaged leucocytes and red corpuscles carried to the gland by the lymph stream being ingested by the endothelial cells lining the sinuses. The same process occurs in the splenic pulp in cases of blood infection. As a sequel to this process of phagocytosis by the non-granular cells, there is a marked diminution of the cells in the peritoneum, and ultimately those left are almost exclusively of the non-granular type. The cells then tend to become smaller, lymphocytes appear and relatively increase in number, and there is a gradual return to the normal condition. There thus occurs first of all a destruction of the organisms by the polymorpho-nuclear leucocytes (microphages), and these cells are in their turn taken up and digested by the non-granular cells (macrophages).

The most striking example of resolution on a large scale is met with in acute lobar pneumonia, in which all the phenomena described above are well seen. Following on the destruction of the organisms, there occur a gradual softening and digestion of the fibrin in the air vesicles, and in this the leucocytes are probably chiefly concerned. The leucocytes and red corpuscles, in great part degenerated, are taken up by non-granular phagocytes *in situ*, or are carried by the lymphatics to the bronchial glands, where they undergo an intra-cellular digestion. If these glands be examined during the process, the lymph tracts and sinuses may be seen to be packed with large cells chiefly of endothelial origin, within which abundant leucocytes and their remains may be present. With the absorption of the fluid contents of the air vesicles, these once more become air-containing, and the part returns practically to normal. Some of the liquefied exudate is got rid of by expectoration, but the amount may not be large, and in every case a large proportion of the exudate is absorbed.

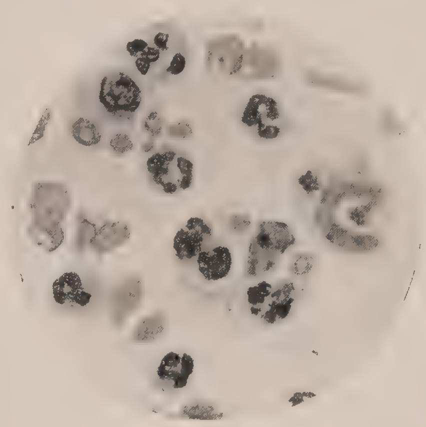

FIG. 34.—Exudate from Peritoneal Cavity of Guinea-pig in resolving acute Inflammation of three days' standing.

Note polymorpho-nuclear leucocytes, also macrophages which have ingested leucocytes and red corpuscles. (D. F. C.) × 500.

Suppuration. While suppuration may be produced by chemical substances under special experimental conditions, it is practically always due to the action of bacteria when it occurs naturally. In the formation of an abscess in an organ or solid tissue, there is a replacement of the tissue by a fluid which we call pus. We have accordingly to consider the nature of pus and how it is produced.

Characters of Pus. The opacity of pus is due to the large number of cells which it contains; when these are thrown down, a clear yellow fluid is obtained—the *liquor puris.* This fluid, which has a specific gravity of about 1030, is essentially blood serum. In addition, there are products of proteolytic digestion; proteoses are present, and even small amounts of amino-acids. When pus is examined microscopically, the great majority of the cells, called 'pus corpuscles,' are seen to be simply polymorpho-nuclear leucocytes, which can be readily identified by the characters of their granules and nuclei. When the pus is recently formed many of these cells may show amœboid movements on the warm stage, but when the pus is older motility is absent, and the nuclei may be degenerated or broken up into granules. A few red corpuscles are usually to be found in pus of recent origin, and may sometimes be so numerous as to give a pinkish tint. There are also non-granular cells in varying proportion, some of which are derived from the blood, others of local origin. Some of the special cells of the tissue in a more or less degenerated condition may likewise be found. Albuminous granules and fatty globules occur, the latter especially in chronic suppuration. In pus of old standing, cholesterol crystals may be present. It is thus seen that pus is essentially an exudate with a large proportion of leucocytes, and containing certain products of protein digestion.

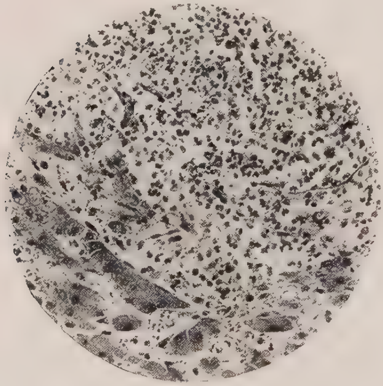

Fig. 35.—Acute Suppuration in Liver, showing masses of Polymorpho-nuclear Leucocytes. Liver cells in lower part of figure are being invaded and destroyed. × 200.

Histological Changes. If the process of suppuration be studied histologically, it is found that two chief changes occur side by side in the tissues, viz. (*a*) a progressive emigration of polymorpho-nuclear leucocytes, which come to pack the tissue, and (*b*) a gradual destruction and disappearance of the tissue elements (Fig. 35). The special cells of the part become necrosed, break down into granular material, then melt away, while the supporting connective tissue fibrils, capillaries, etc., are digested and disappear. The accumulation of leucocytes still going on, the tissue gradually becomes replaced by pus, in which some of the remains of the destroyed tissue may be present. In suppuration there is thus an actual destruction of tissue, and a return to normal is no longer possible. It differs from simple necrosis in there being a gradual digestion of the tissue accompanied by leucocyte accumulation, whereas in simple necrosis the tissue may retain its structural outlines for a long time.

Nature of Phenomena. The progressive emigration of leucocytes is due to a continued supply of chemotactic substances from the bacteria, and, although the pyococci are most frequently concerned, suppuration may be produced by a great variety of organisms, the essential point being that they should be able to persist in the tissues and produce their effects. With regard to digestion or liquefaction of the tissues, it may be stated that this is chiefly due to proteolytic enzymes produced by the leucocytes, these enzymes acting on the tissues previously damaged by the bacteria. Some of the pyogenic organisms have a digestive action on proteins, as is shown by their liquefying gelatine, but others such as streptococci and pneumococci, which are scarcely less active in producing suppuration, have no such property. The digestive softening of the tissues by the leucocytes follows on the damage or actual necrosis due to the bacterial toxins, as there is no evidence that leucocytes, however numerous, will attack normal tissues. Digestive action by the leucocytes is seen also when suppuration has been preceded by much exudation of fibrin, e.g. in pleurisy. The fibrin is to a large extent digested and disappears, and this is closely analogous to the action of the leucocytes in removing fibrin in the process of resolution of inflammation, as is seen, for example, in pneumonia. In the case of dense tissues, complete suppurative softening may be interfered with by the density of the tissue; and a portion of dead tissue or slough may form, and may persist for a considerable time. This is well exemplified by a boil on the skin, where the core is constituted by a necrosed portion of the cutis.

When suppuration ceases to spread, there occurs at the periphery a reactive proliferation of the connective tissue cells, with new formation of blood vessels; in other words, a zone of granulation tissue forms around it. This becomes denser in its outer part, and thus a definite wall to the abscess is formed—the so-called ‘ pyogenic membrane.’ If the abscess is of small size, the pus may become absorbed and a small cicatrix result. The pus may, however, be too abundant for this to occur, and then it becomes thickened and changed into granular débris, in which at a later date lime salts may be deposited; in the case of a chronic empyema, large calcareous plates may be formed in the pleural cavity. Further, the longer the accumulation of pus lasts the greater will be the thickening around, and, accordingly, any abscess cavity ought to be opened so that the evacuation may allow the walls to come together and healing to occur with the minimum of fibrosis. When an abscess forms near a free surface, for example in the subcutaneous tissue, the tension of the contents causes the suppuration to extend in the direction of the surface so that the overlying skin becomes involved. The abscess is then said to ‘ point ’ and it may ultimately discharge its contents spontaneously.

Catarrhal Inflammation. The term was originally applied to an inflammation of a mucous membrane accompanied by increased discharge of secretion. In such a condition the surface epithelium becomes damaged and desquamated, whilst as a result of this, proliferation of the surviving cells and an attempt to repair the damage follow. The term has accordingly been applied to similar changes in epithelium generally. Thus we speak of a catarrhal nephritis when the important damage falls on the tubules and reparative change follows. When a chemical irritant is applied to a mucous membrane, the increased flow of secretion may dilute and remove the irritant. But in other cases, and especially when the cause is of bacterial nature, the irritant may persist and bring about inflammatory changes in the mucous membrane. The secretion varies in different conditions, but there is an increased formation of mucin which may be in a tough concentrated form, or may be greatly diluted and watery; usually the amount of albumen present is small. Sometimes, as in nasal catarrh, the discharge may be very profuse; and another striking example of this is the very abundant intestinal discharge in cholera. In severe cases of catarrh the secretion may be reddish, owing to the admixture of red corpuscles. At first it is relatively clear, but as leucocyte emigration is established, it becomes more opaque and ultimately muco-purulent. This last condition is usually associated with loosening or diminution of the tenacity of the mucus, apparently the result of leucocyte action. The epithelial cells become damaged and separated to a varying degree; single cells may be desquamated, but sometimes sheets of epithelium become loosened and set free, as is well seen in severe bronchitis (Figs. 36, 37). The surviving cells undergo a reparative proliferation; the young cells may in their turn be desquamated, and the two processes of loss and repair may go on for a time. Ultimately complete repair may be effected. In the case of the bronchi, small oval or pear-shaped cells can often be seen on the basement membrane; these are survivors of the deepest layer and take an active part in the repair. While such changes are occurring in the epithelium, the usual phenomena of inflammation are to be seen in the subjacent connective tissues. There is marked vascular engorgement with emigration of leucocytes, etc., and these cells pass through the basement membrane in increasing numbers, and mingle with the secretion, sometimes giving it a purulent character, as has been stated.

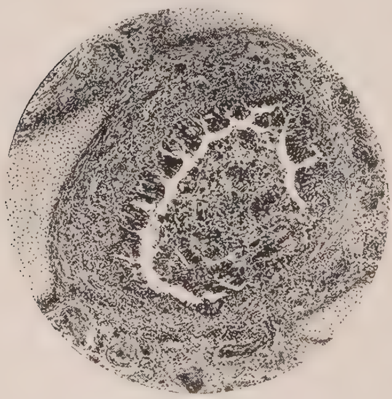

FIG. 36.—General View of Bronchus in Acute Inflammation. The lumen is filled up with desquamated epithelium and purulent exudate. × 45.

Results of Acute Catarrh. If the inflammation does not completely resolve, but passes into a chronic condition, then structural changes take place in the connective tissue of the mucosa and underneath, which make a complete return to normal impossible. There is proliferation of connective tissue cells with formation of new vessels, in fact the formation of a layer of vascular granulation tissue, which may cause considerable swelling and often unevenness of the mucosa. In the case of chronic catarrh of the stomach, the epithelium in the upper portion of the glands may be entirely lost, and the superficial part of the mucosa may be chiefly granulation tissue. At a later stage still, the connective tissue becomes more fibrous and contracts, and the mucous membrane passes into an atrophic condition. In chronic catarrh, the ducts of glands may become occluded, and small retention cysts are formed, whilst in some situations, e.g. stomach and cervix uteri, small papillomatous growths from the mucous membrane are not uncommon. It will be clear from what has been said that the efficient treatment of catarrh in the acute stage is of great importance, so that a return to normal as far as possible should be obtained and the later structural changes avoided.

Leucocytosis. Any conception of inflammation merely as a local process would be very incomplete. When there is an inflammation of some extent a leucocytosis is present in the blood, that is, there is an increase of leucocytes, the number often reaching 25,000 per c.mm. or even more ; and this increase is chiefly on the part of the polymorpho-nuclears—the cells which emigrate most actively from the vessels. We have accordingly to consider the means by which the supply of these cells is maintained. In an acute pneumonia, for example, the number of leucocytes which pass into the affected lung in the course of a few days may be several times the total number of leucocytes in the blood. And in view of the large amounts of pus which in certain conditions may be discharged constantly for a long period of time, the supply of these cells would appear to be practically unlimited.

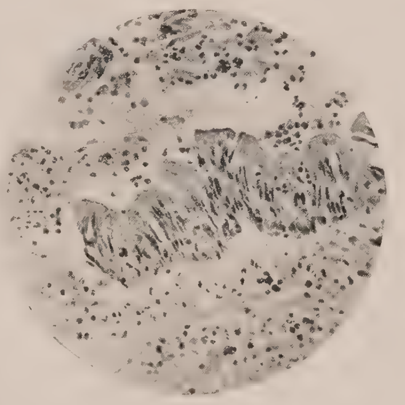

Fig 37.—Portion of Wall of Bronchus in acute Inflammation, showing Desquamation of Epithelium and Leucocytic Infiltration. × 200.

The subject of leucocytosis will be considered later in detail ; we shall give here only the main facts bearing on the above questions. It is now thoroughly established that the finely granular polymorpho-nuclear leucocyte is derived from a larger cell with similar granules, but with rounded or oval nucleus—the finely granular or neutrophile myelocyte, which occurs in large numbers in the red bone-marrow (Fig. 38). This cell divides by mitosis, producing smaller daughter cells, the nuclei of which become indented or horseshoe-shaped, and ultimately assume the characteristic polymorphous type. When the myelocytes are stained by such a stain as Jenner's, their protoplasm is coloured a pale blue, that is, has a feeble basophile reaction, whilst the granules give various tints, from purple to red. In the daughter cells the basophile reaction of the protoplasm gradually disappears, and the granules come to stain a uniform red colour. In the 'ripening' of the polymorpho-nuclear cell, as it is sometimes called, there are accordingly changes in the configuration of the nucleus and in the reactions of the protoplasm and granules. In the young polymorpho-nuclears in the marrow the nucleus shows relatively simple lobation but after the cells have passed into the circulating blood the lobes increase in number and become more separated. (In Fig. 38 the lobation of nucleus represented in cell *c* in marrow is too marked.) In this way the relative age of the cells can be recognised, as will afterwards be described (p. 444).

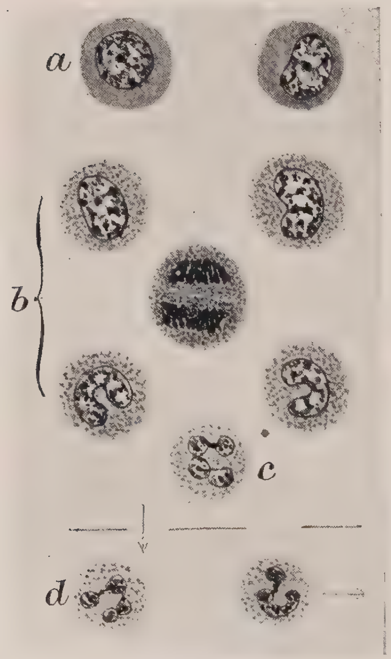

Fig. 38.—Diagram illustrating Formation of Polymorpho-nuclear Leucocytes.

a, myeloblasts; *b*, finely granular myelocytes; *c*, polymorpho-nuclear leucocytes in bone-marrow which pass into blood stream (*d*).

In normal conditions there is what may be called a reserve supply of polymorpho-nuclears, which lie at the periphery of the blood stream in the marrow. There is thus a mechanism for the addition of an increased number of these cells to the general circulation, and this is the initial stage in the production of leucocytosis. Leucocytosis can thus be readily produced, quite apart from any local inflammation, by the injection of various chemotactic substances into the blood stream, e.g. peptone, cinnamic acid, etc. When this is done, there is at first a leucopenia, due to an accumulation of the leucocytes in the capillaries of internal organs, and not to a destruction of the cells as was at one time supposed; and this is followed within a few hours by leucocytosis. If, however, the demand for leucocytes is maintained, there then occur an active proliferation of the myelocytes and increased formation of polymorpho-nuclears. The marrow proper increases as a whole, while the fat diminishes in a corresponding degree, and the myelocytes come to constitute an increased proportion of the marrow cells (Figs. 39, 40). This change, which is known as a *leucoblastic* reaction, forms a contrast to the *erythroblastic* reaction in which there is increase of erythroblasts in response to demand for red cells, e.g. after hæmorrhage. In the case of the human subject, moreover, there is not only this change in the red marrow of the short bones, but there is also a remarkable reaction in the yellow marrow of long bones. Latent foci of marrow lying between the fat cells become stimulated to proliferation, and also new foci are formed from cells of the reticulo-endothelial system. These rapidly extend, and ultimately there is considerable replacement of the fat by active hæmopoietic marrow. In the femur, for example, after an acute pneumonia of a few days' standing, a considerable proportion of the yellow marrow may be thus changed into red marrow, the reaction starting at the upper end and extending downwards. In this newly formed marrow all the constituent elements of normal red marrow are present, but the increase is specially on the part of the myelocytes. The increased supply of polymorpho-nuclear leucocytes is thus provided for.

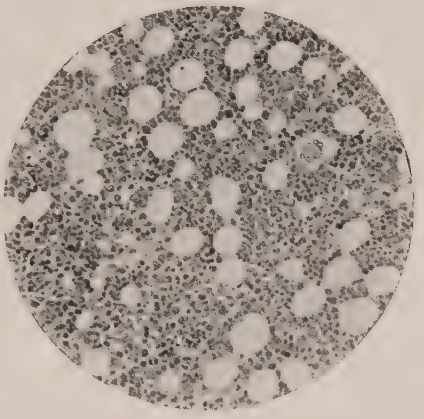

Fig. 39.—Bone-marrow of Rabbit after Leucocytosis of moderate degree, showing distinct increase of the Cellular Marrow with diminution of the Fat Cells. × 150.

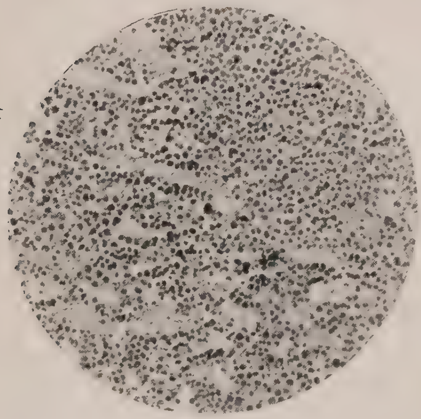

Fig. 40.—Bone-marrow of Rabbit after long-standing Leucocytosis. The fat cells have practically disappeared and been replaced by a cellular tissue in which the great majority of the cells are myelocytes. × 150.

In the normal marrow, along with the finely granular cells there are to be seen similar cells but with protoplasm more basophile and free from granules—the myeloblasts (Fig. 38). All stages of transition between myeloblasts and myelocytes can be found, and this is the case also when cells of the myelocyte series enter the blood in leukæmia. Increased supply of leucocytes might accordingly be provided for by increased proliferation of the myeloblasts, with subsequent transition through the myelocyte stage to the polymorpho-nuclear leucocytes. Our results both of experiments and of observations on the human subject, however, show that in the adult, at least, the cells usually found undergoing mitotic division contain distinct granules, and that thus the supply of leucocytes is kept up by a proliferation of myelocytes rather than of their non-granular precursors.

In some very severe infections leucocytosis may be absent,—there may even be a leucopenia—and a few myelocytes may appear in the circulation. In such a condition there is a failure of the leucoblastic reaction of the marrow; myelocytes may be actually diminished, and their place taken by an increased proportion of red corpuscles. Some of the myelocytes may show degenerative changes. Such a condition, which is well seen in hæmorrhagic smallpox, may be described as a *depleted state* of the marrow, evidently the direct result of toxic action, and explains readily the non-occurrence of leucocytosis. In acute pneumonia in alcoholics leucocytosis may be absent, or there may be even leucopenia, and here also there is a failure of the hyperplastic response in the marrow. The different conditions of the marrow are more fully considered later (p. 515). Increased formation of *eosinophiles*, with increase of these cells in the blood or *eosinophilia*, results in a similar way from a more active proliferation of eosinophile myelocytes.

Varieties of Cells in Inflammatory Conditions. The following facts may be stated with regard to the parts played by the various kinds of cells in inflammation.

Polymorpho-nuclear Leucocytes. As already explained, these cells have a definite and single origin, namely, from the finely granular myelocytes of the bone-marrow, and it is to be noted that normally they are practically absent from the connective tissue spaces. They are the cells which emigrate most actively and in largest numbers in most acute inflammations; in fact they are the cells chiefly concerned in infections by the so-called pyogenic organisms—staphylococci, streptococci, pneumococci, B. coli, etc. So long as the organisms persist in the tissues the emigration of leucocytes continues, and suppuration (p. 73) may follow, when these cells become the ordinary pus corpuscles. In acute catarrhal inflammations also, they abound and become mingled with the secretion, being specially numerous when this is of purulent character. They are actively amœboid and phagocytic, and have proteolytic properties by means of a protease which they form. There is evidence that, as Metchnikoff held, they are the source of various defensive substances, bactericidal and opsonic, which they set free in the surrounding lymph. The polymorpho-nuclears undergo increase also in the blood during an inflammation of some extent; this phenomenon has been discussed above. It must be recognised that the polymorpho-nuclears are found also in the tissues around dead or degenerate material, where none of the other characteristics of an acute inflammation are present, and they play an important part in its digestion and absorption. On the other hand, in certain acute inflammations of which the intestinal and lymphatic lesions in typhoid are the most striking example, there is little emigration of polymorpho-nuclears, the reaction being mainly on the part of the non-granular cells (Fig. 42). And in inflammatory œdemas, for example those produced by the B. welchii and the bacillus of malignant œdema, polymorpho-nuclears are again scanty.

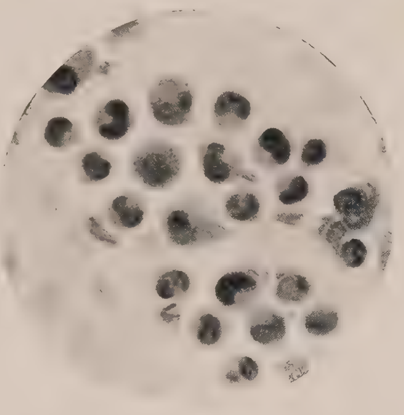

Fig. 41.—Film Preparation from Marrow shown in Fig. 40, showing finely granular Myelocytes and Transitions to Polymorpho-nuclear Leucocytes. × 400.

Non-granular Wandering Cells or Macrophages : Reticulo-endothelial System.[1]—The characters of these cells and their activities were observed and described by Metchnikoff at an early stage in his studies on phagocytosis, and he applied to them the term *macrophages* (in contrast to the *microphages* or finely-granular leucocytes). He insisted on their importance in the phagocytosis of damaged cellular elements, of protozoa, and of certain more slowly growing bacteria, e.g. *B. tuberculosis*, *B. lepræ*, etc.; and he believed that they were the source of the immune-bodies which develop in active immunisation (p. 189). It soon came to be recognised, however, that macrophages are not a homogeneous class but include several varieties, e.g. mononuclear cells of the blood or monocytes, histiocytes, derivatives of the endothelium of lymph channels and certain blood capillaries, cells of reticulum, etc. The source of cells of this class may sometimes be

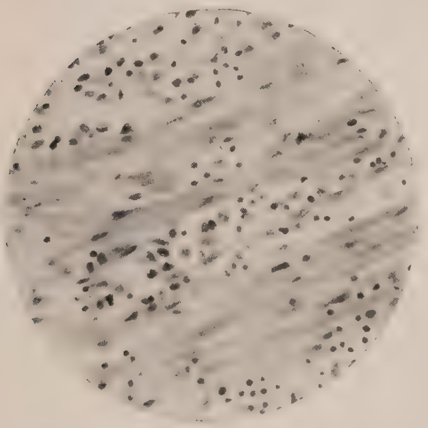

Fig. 42.—Acute Inflammation in Typhoid Fever, showing Infiltration of Muscular Coats by Mononuclear Cells and Lymphocytes. × 250.

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[1] See *Lectures on Pathology*, by L. Aschoff, New York, 1924.

traced by histological methods, especially under experimental conditions. But after a time they may lose their characteristic features and in many lesions occurring naturally it may be impossible to discriminate different kinds of macrophages and to assign their origin. The use of some general term, such as macrophages or non-granular wandering cells, is thus often convenient in describing pathological conditions.

Within recent years the method of vital staining—that is the staining which results from the injection of a dye *intra vitam*—has led to extensive research on this question. A number of stains have been used for the purpose, for example lithium carmine, trypan blue, isamin blue, etc., and when one of these is injected intravenously it is found that certain cells are coloured deeply, others faintly, others again not at all. The cells which stain deeply have therefore the peculiar property of taking up in considerable amount the stain in solution without being damaged in consequence, and the stain is then deposited in their interior in the form of granules (Fig. 43). Aschoff and Landau observed that the property of being deeply stained was shown especially by certain endothelial cells and reticulum cells and by some of the macrophages derived from them; they accordingly applied the term *reticulo-endothelial system* to the tissue cells which are vitally stained and also to their derivatives which show the same property. The cells of this system comprise both relatively fixed cells and also wandering cells. The chief examples of the former are (*a*) the reticulum cells of the splenic tissue, of the bone-marrow, and of the nodes and cords of lymphoid tissue, and (*b*) the endothelial cells of the splenic sinuses, lymph channels, liver capillaries (Kupffer cells), capillaries of bone-marrow and also of the adrenals and hypophysis. The distinction between reticulum cells and endothelial cells is convenient but must not be sharply maintained as the two types are sometimes apparently the same. There is evidence, for example, that certain endothelial cells, e.g. those of the hepatic capillaries and splenic sinuses, can also form reticulum. In addition to the cells mentioned as constituting the reticulo-endothelial system, there occur also widely distributed in the tissues cells which react in a similar

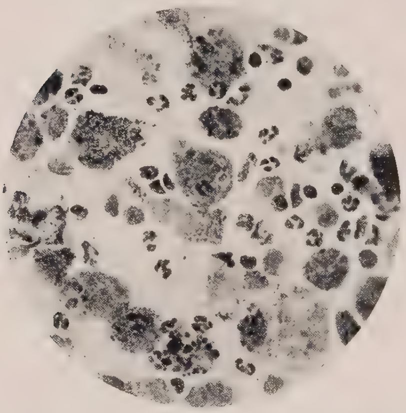

Fig. 43.—Vitally stained Cells from Peritoneal Cavity of Rabbit several days after injection of a Dye (Diamine fast scarlet). (D. F. C.)

Note numerous macrophages containing granules of the dye along with polymorpho-nuclears which are free from granules. × 400.

manner. Ranvier described in loose connective tissues, notably of the omentum, certain cells of varying forms which he called *clasmatocytes* and regarded them as belonging to the leucocyte class. Later, however, Marchand showed that they belonged to the connective tissue class and called them *adventitial cells*, because they are abundant in the sheaths of blood vessels. Such cells are usually oval or somewhat spindle-shaped, not infrequently with branching processes. Their protoplasm is somewhat finely granular, stains more deeply and is more defined than that of the connective tissue cells or fibrocytes. Such cells, though occurring especially in the positions mentioned, have a wide distribution in the connective tissues ; they are now generally believed to be the descendants of migratory cells derived from mesenchyme cells and are now usually known as *histiocytes*. In inflammatory conditions they rapidly assume the round form of macrophages and become actively phagocytic. They are also readily stained by the intra-vitam method and are included as part of the reticulo-endothelial system. It may be added that, in contrast to the histiocytes, the ordinary connective tissue cells or *fibrocytes* stain only faintly by intra-vitam methods, while any stained granules in them are small. When inflammatory foci are present in the body of an animal and a suitable dye is introduced into the circulation, the foci become deeply stained owing to the presence of the large numbers of cells which take up the dye, and thus may be recognised by the naked eye. This fact has been found of service in aiding the recognition of small foci of inflammation in experimental conditions.

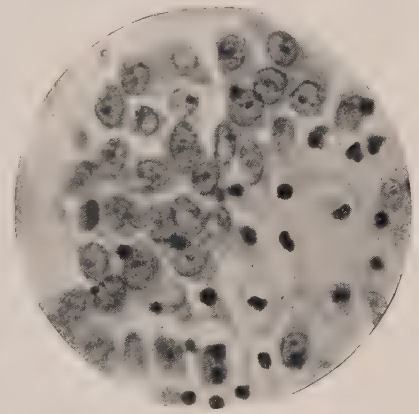

Fig. 44.—Section of Peritoneum in subacute Inflammation, showing the Characters of the Serosal Cells, which have proliferated. (Prof. J. S. Young.)

In lower part of figure, some of the cells have undergone necrosis and their nuclei are pyknotic. × 750.

Serosal Cells. In acute inflammation the *serosal cells* of the large sacs usually become desquamated at an early stage and the free cells can be recognised for a time in the exudate. In less acute conditions, they may undergo proliferation and occasionally form sheets of considerable thickness on the serous surface (Fig. 44). Ordinarily they show no evidence of taking part in the formation of connective tissue, but we have indications of this in certain instances, there being all transitions between typical serosal cells on the surface and cells forming fibrils below. Such an appearance may be deceptive, but I believe that sometimes they may form connective tissue, though usually there is no trace of this. The accompanying figure (Fig. 45) shows the characters of serosal cells and fibroblasts as seen in tissue culture.

I formerly believed that the serosal cells were actively phagocytic towards damaged leucocytes, etc., but I am now convinced, in agreement with most recent observers, that they have little or no phagocytic action. The cells which are so active in phagocytosis are mainly histiocytes which have wandered into the serous sac. The monocytes participate also, though in less degree. It may be added that, in the presence of certain irritants, serosal cells may undergo metaplasia and form cells of different types and of varying arrangement (p. 125).

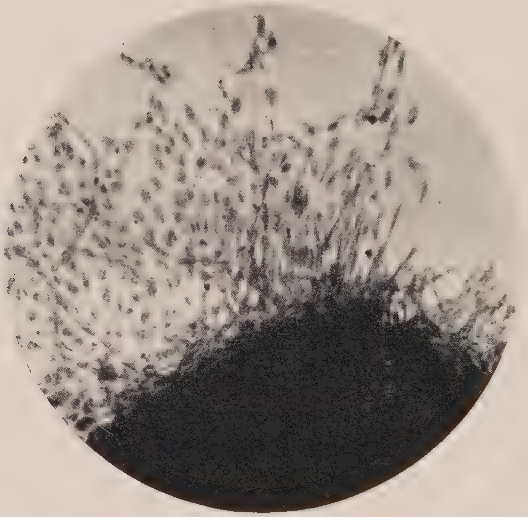

Fig. 45.—Tissue Culture Preparation showing a sheet of Serosal Cells and also outgrowing spindle-shaped Fibroblasts. (Dr. Janet S. F. Niven.)

It is to be recognised that the two classes of cells, monocytes and histiocytes, seen in active lesions, cannot be distinguished by ordinary stains. By the use of the so-called supravital methods—the addition of dyes such as neutral red, Janus green, etc., in weak solution to fresh exudates—morphological differences can be brought out which enable a distinction to be made. Thus, for example, the monocytes have in their cytoplasm a group of granules stainable by neutral red arranged like a rosette round the centrosome, whilst in the histiocytes the stainable granules are diffusely scattered through the protoplasm. Even in fresh preparations made under experimental conditions, while many cells conform to the two main types others present intermediate characters and their differentiation seems to us a matter of great difficulty.

The conception of the reticulo-endothelial system has been of great service in bringing into prominence a group of cells with special properties in relation to the storage of chemical substances and phagocytosis. It must be recognised, however, that it is not a sharply defined system either anatomically or physiologically. For example, some parts of the vascular endothelium are included while most are not; and then again in conditions of special demand the storage and phagocytic functions are taken up by other cells outside the 'system.' The term should be recognised as one of convenience but not capable of accurate definition; and the determination of what should be included ought to be a matter of agreement and compromise. While the functions of the system come into evidence chiefly in abnormal states, it is now established that it is the main seat of the normal formation of bile pigment. This subject will be discussed at a later stage. In various conditions of disease the system also plays an important part in the storage of lipoids (pp. 499 501), blood pigment, etc.

Lymphocytes and *Plasma Cells*. The lymphocytes have feeble amœboid powers, but there is little doubt that they also emigrate from the blood vessels. This is well illustrated in the case of certain inflammations, for example in acute lethargic encephalitis, where they emigrate and may form large collections around the blood vessels (Fig. 460). It can hardly be said that they have no phagocytic power, but this is at a minimum. Probably they become enlarged when they are going to exert this function. Although they occasionally migrate in fairly acute conditions, they accumulate in the tissues especially in chronic inflammations, or where a more active reaction has become quiescent. They are often numerous around tubercle follicles, also in the interstices of cicatricial tissue, and often form collections of considerable size where epithelium is undergoing involution and atrophy, for example, in the thyroid gland in myxœdema, in cirrhotic lesions of the liver and kidney, etc. They abound also around the cells of an invading epithelioma or other growth, and there is evidence that development of immunity against malignant growths is associated with special activity of these cells. They probably represent a response to the mildest types of irritation, but their precise function is not known.

The *plasma cells*, which have a characteristic appearance, are often found in subacute and chronic lesions along with lymphocytes, but they tend to abound in rather more active lesions than the latter. They are somewhat larger than lymphocytes, and their protoplasm is more abundant and more basophile. The nucleus is spherical, usually eccentric in position, and possesses a coarse chromatin network, the threads of which are arranged in a radiate fashion—'cart-wheel' or 'clock-face' type of nucleus. At the side of the nucleus there is often a narrow unstained crescent. With Pappenheim's methyl green and pyronin stain the protoplasm of the plasma cells is stained a distinct red colour. They are feebly amœboid and rarely phagocytic. There is little doubt that they are usually derived from lymphocytes, and probably may assume the characters of the latter again. Their characters are well shown in Fig. 46. Plasma cells are seen in granulating wounds and in subacute and chronic inflammatory lesions.

They are usually abundant in syphilitic lesions, both in the primary sore and in the later lesions, e.g. around gummata, in syphilitic mesaortitis, etc. Their functions cannot be satisfactorily defined, but evidently include a protective property. They probably represent a more active type than the ordinary form of lymphocyte.

Eosinophile Leucocytes. These are known to accumulate in certain diverse conditions. They abound in the sputum in bronchial asthma, in certain skin lesions, e.g. pemphigus, psoriasis, etc., and around animal parasites, for example the *Trichinella spiralis*. In the lesions of lymphadenoma they are often numerous, and they are occasionally abundant in various tumours, but in such conditions their presence appears very variable. In view of the diversity of conditions, it is not possible to make a statement as to any one general influence which regulates their appearance in the tissues. The eosinophiles are actively amœboid, but rarely, if ever, phagocytic. The view put forward by some that the granules represent a secretion of defensive nature, which becomes discharged, has not been established. In conditions where there is an emigration of eosinophiles into the tissues, notably in parasitic diseases, increase of these leucocytes or *eosinophilia* is present in the blood ; this is produced in the same way as ordinary leucocytosis.

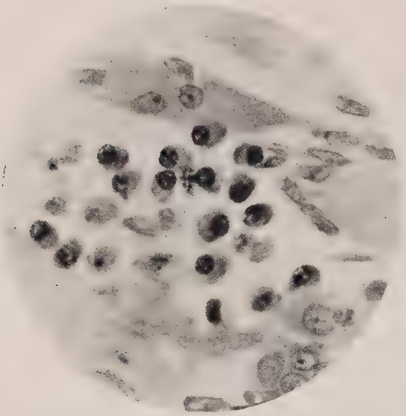

FIG. 46.—Plasma Cells in subacute Inflammation, showing the abundant Protoplasm and characteristic Nuclei. (G. H. W.) × 600.

Fibroblasts. These are spindle-shaped or oval cells, often with delicate processes at their extremities, and are formed by enlargement of the pre-existing connective tissue cells or fibrocytes (p. 66). They appear at an early stage of inflammation and become very numerous and active in the process of repair (p. 109). They usually have a quite distinctive appearance and are in ordinary circumstances probably the only cells which actively form collagenous fibres. We put the statement in this form advisedly, as it is not possible to speak dogmatically and there is left open the possibility that serosal and other cells may in some circumstances take part in the formation of connective tissue. The fibrocytes may be regarded as a distinct cell lineage which is split off from mesenchyme cells at an early stage of development, and their functions are mainly formative. Another cell lineage ,of similar origin is constituted by the histiocytes, which are widely distributed and whose functions are chiefly phagocytosis and storage. The characters of fibroblasts are well shown in Fig. 47.

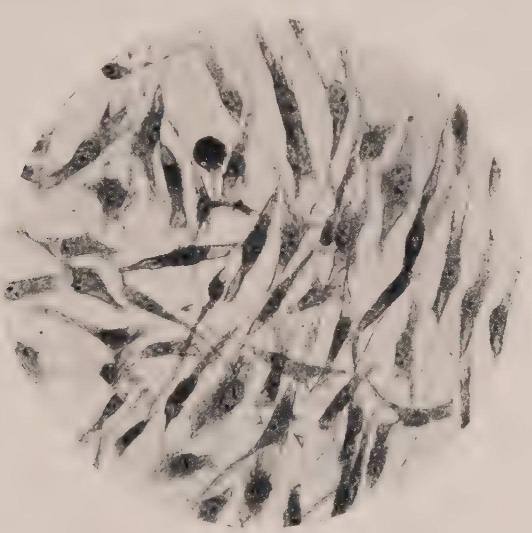

FIG. 47.—Fibroblasts as seen in a Culture *in vitro*. (Dr. Janet S. F. Niven.) × 300.

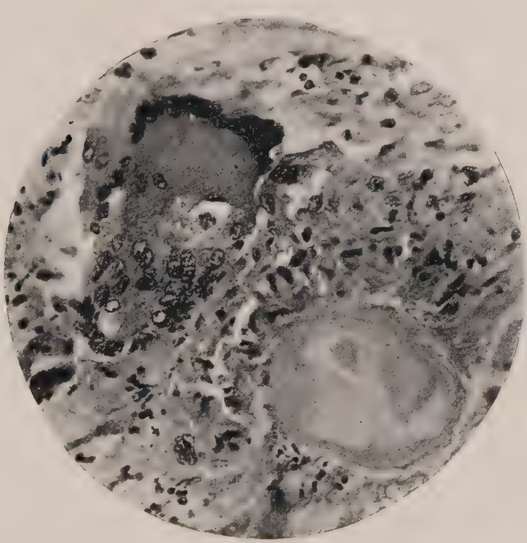

FIG. 48.—Section of Nodule from Peritoneal Cavity, showing large Foreign-body Giant-cell and Proliferation of Macrophages around Foreign Body, probably a Fruit Seed, which is seen as a structureless mass to the right of figure. (D. F. C.) × 300.

Giant-cells. Metchnikoff showed that the fusion of cells to form multi-nucleated plasmodial masses is a common phenomenon throughout the animal kingdom. Corresponding cells are frequently met with in various pathological conditions in the human subject and are called *giant-cells* or foreign-body giant-cells. Such cells, which may reach a considerable size, vary greatly in form, and have often an irregular or branched outline; they contain multiple small oval nuclei which are usually pretty uniform in appearance (Figs. 48, 49). The number of nuclei is sometimes very great. Much discussion has taken place as to their origin, but it seems certain that they may be derived from different kinds of cells. In fact, plasmodial formation seems to be a throwing back to a primitive property possessed by cells. Their chief origin is from cells of the reticulo-endothelial system, but we believe that they originate also from connective tissue cells, and even from epithelial cells. We have, for example, traced the formation of giant-cells from the epithelium in the thyroid, parotid, and the ducts of the mammary gland. Their mode of formation likewise appears to vary, as in some cases the multinucleated condition is the result of amitotic division of the nucleus of a single cell, whereas in other cases the giant-cell is formed by fusion of several cells. The former mode, however, seems to us to be the more frequent in the human subject. In a general way, giant-cells may be said to form especially around material which is difficult of absorption. They are thus seen around such substances as cholesterol crystals, urates, and sometimes fatty and degenerated material. They are common in old wounds, where they have formed in relation to catgut or silk fibres, and they can be readily produced by the injection of such substances as solid paraffin or agar into the tissues. The giant-cells which are so common a feature of tuberculous lesions, are to be regarded as belonging to the same class; as are also those met with in syphilis, although in this latter condition giant-cells occur less frequently, and are usually of smaller size.

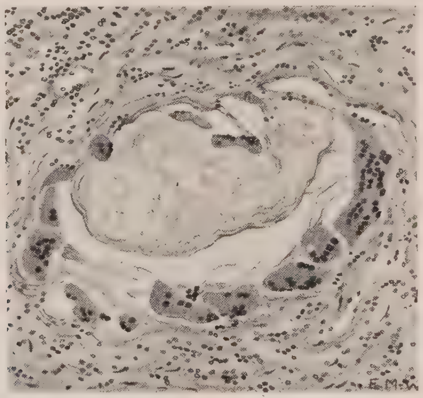

Fig. 49.—Giant-cells around Keratinous Mass formed by excessive Cornification of Nodule of Epithelioma. (M. J. S.) × 100.

Other Varieties. Whilst these are the main varieties of cells which can be readily recognised in inflammatory processes, reference may be made to some others which have been described. The term *polyblast* was applied by Maximow to cells of mononuclear type with basophile protoplasm, which often abound in inflammatory conditions. He considered that they are derived in part from the larger lymphocytes, and in part from histiocytes. He held also that the polyblasts may assume different characters and become plasma cells, macrophages or giant-cells, and may even in certain circumstances take part in the formation of connective tissue. The term *mast-cell* is applied to a cell containing coarse basophile granules, which usually give a metachromatic reaction with methylene blue. Mast-cells are met with along with adventitial cells, and some of them may be derived from the latter. Others again may have come from the blood. According to the recent results of Jorpes and others, the mast-cells are important carriers of heparin ; in fact the granules are largely composed of this substance, and to it the metachromatic reaction is due. Heparin is a polysulphuric ester of high molecular weight and is well known as a natural anticoagulant. It is not possible as yet to say what light these results will throw on the part played by mast-cells in pathological conditions.

In recent years, a large amount of research has been carried out with regard to the genetic relationships of the different kinds of cells which we have discussed. No general agreement, however, has been arrived at, and it is not possible to say to what extent transition from one type of cell to another takes place. All are agreed that the differentiated granular leucocytes are end-products and undergo no change into other types, but with regard to the non-granular cells diversity of opinion still prevails. In pathological conditions, macrophages (monocytes and histiocytes), lymphocytes along with plasma cells, serosal cells and fibroblasts are concerned in different processes and behave very much as if they constituted different classes. But whilst this is so, it must be freely admitted that transitions between the different types may take place. The position seems to be pretty much the same as that in connection with the cells of the blood. Under normal circumstances cell production is of the homoplastic type, that is, each cell is formed from a definite mother cell or ancestor ; but in pathological states it may be carried back to an earlier stage in ontogenetic development, and then we see cells undergoing differentiation into other types which ordinarily are quite distinct.

CHAPTER III

INFLAMMATION (*continued*), REPAIR AND HYPERTROPHY

Introductory—Proliferative Processes in General

The proliferation of cells constitutes so important a factor in chronic inflammation and other pathological conditions to be considered afterwards, that it will be of advantage to give at this stage a general survey of the circumstances under which it occurs. In the adult body, in the normal state, cellular proliferation is practically in abeyance, except in the case of those tissues whose cells are constantly being lost. Cells are continually being lost by desquamation from the skin surface and from mucous membranes, and there is a corresponding proliferation to make good the loss. Red blood corpuscles and leucocytes are constantly undergoing disintegration, and accordingly we find signs of active division in the cells in the germ centres of lymphoid tissue and in the bone-marrow. In any case, cellular proliferation in the adult is a process of what we may call normal repair. But in internal organs, such as liver, adrenals, kidneys, etc., we have a state of cellular equilibrium and practically no proliferation. In certain pathological conditions, however, proliferation may be set up in cells normally in a quiescent state, and also may be increased in the tissues where cell multiplication normally occurs. The following are the *chief* of these conditions, but there are some examples of proliferation to be mentioned which cannot be placed in the categories given :—

(1) *Wounds or Destruction of Tissues.* In such conditions a process of reparative proliferation comes into action, and the important factor in initiating the process is *breach of continuity.* Under normal circumstances all the cells of the body have a relation to the surrounding cells, and this relation, in the case of solid tissues generally, is on every side ; in the case of the superficial cells of epithelia and endothelia, on every side but one. This relationship acts as a restraint on cell proliferation ; it produces what is often known as tissue tension. Disturb this relationship, say by a cut, and the cells in the neighbourhood proliferate in order to restore the relationship ; once this is effected the proliferation comes to an end. If, on the other hand, the breach is maintained by repeated damage or loss, the cells will continue to multiply, and there appears to be practically no limit to the proliferative capacity. The process of repair will be

studied more fully later, but at present it may be stated that the proliferative capacity varies much in the case of different tissues, being as a rule inversely in proportion to the degree of specialisation. Thus it happens that repair in a highly developed tissue is often effected by one of lower order, especially by fibrous tissue.

Repair following upon loss is well illustrated in the case of the blood, the occurrence of hæmorrhage leading to increased proliferation of the erythroblasts in the bone-marrow. In this case, however, the matter is more complex, as the proliferation is the result of diminished oxygen supply, which acts in some way as a stimulus. Further, when the condition of diminished oxygen supply is maintained, for example when a person lives at a high altitude with diminished oxygen tension, a compensatory hyperplasia of the erythroblasts occurs and the number of red corpuscles in the blood per c.mm. is raised above normal (p. 434).

(2) *Chronic Irritation.* Cell proliferation is an outstanding feature of the reaction which occurs when the tissues are exposed to the action of irritants of a milder nature, in fact, irritants insufficient to produce the death of the cells or marked exudation. It is thus a chief phenomenon of chronic inflammation. Here again it is the less highly specialised tissues which react most. Such proliferation is closely allied to that following breach of continuity or damage; it is often impossible to draw the line. For example, necrosis of tissue means a breach of continuity so far as the surrounding living cells are concerned, and at the same time the dead tissue may act as a mild irritant. It is possible that in both cases a substance of the nature of H-substance (p. 13) is set free from the affected cells and this acts as the stimulus to proliferation. As yet, however, it is not possible to pronounce definitely with regard to this.

(3) *Functional Hypertrophy* and *Hyperplasia.* Cellular proliferation may occur as a response to increased functional demands. Increased katabolism beyond the normal (within limits, of course) leads to increased anabolism and thus to enlargement or hypertrophy of cells. The hypertrophied cells then may undergo multiplication, and as a result of these two processes the functioning tissue becomes enlarged. The peculiarity in this type of proliferation is that the *specialised cells* of an organ can be called into formative activity while the stroma is unaffected.

(4) *Growth produced by Special Stimuli.* It is now known that the internal secretions of certain endocrine glands act as direct stimuli to growth. The excessive growth seen in giantism and acromegaly caused by hyperactivity of the anterior lobe of the hypophysis, has come to be recognised as an example of such an effect, and the complete experimental proof has recently been provided (p. 918). Again, the hyperplastic changes in the mammæ in pregnancy are brought about by a hormone supplied by the corpus luteum or by the tissues of the fœtus; and the hyperplastic changes in the endometrium in

the menstrual cycle are similarly brought about by hormones. The existence of true stimuli to growth as distinguished from necessary food stuffs must thus be recognised. It is generally regarded that the favouring influence of embryonic juice on growth in tissue cultures is due to the presence of growth-promoting substances. This view has been extended by Carrel to the process of repair in general and he has given the name *trephones* to such substances, of which he believes that the leucocytes are an important source. But it has not been shown that the application of such substances, supposed to act as stimuli, leads to a proliferation of cells when they are in their normal relationships. The subject of chemical agents in relation to growth is one of high importance but it is little understood. What we know, however, with regard to the remarkable effect of hormones, notably those of the ovaries, in promoting and regulating tissue growth opens up wide possibilities ; and the recent work in experimental embryology with regard to the part played by ‘ organisers ’ in development has given results of even more striking character.

There are thus three main conditions in which *reactive* proliferation is called forth, and it is to be noted that in the processes of repair and chronic inflammation, the proliferation is mainly on the part of stroma cells and non-specialised epithelia, while in the case of functional hyperplasia the specialised cells are those concerned. The growth produced by hormones and like substances may be regarded as in a category by itself, and it is to be noted that both types of cells, specialised and non-specialised, may be affected by such action. The proliferation occurring in tumour growth or *neoplasia*, so far as is known, is of a different character and will be discussed later.

CHRONIC INFLAMMATION

The lesions in chronic inflammation are characterised by proliferation of fixed cells of the part, and by new formation of blood vessels, whilst the wandering cells present are chiefly of the non-granular series—we may say, chiefly macrophages, plasma cells, lymphocytes and also giant-cells. Reaction of this type is often spoken of as *productive* inflammation in contrast with the *exudative* inflammation of acute type. These terms are convenient as indicating the predominance of one of two different processes, but it must be recognised that these processes are met with together in varying proportion.

We have seen that even in an early stage of acute inflammation, some proliferation of the connective tissue cells occurs. As the irritant becomes less intense in its action, this change is more marked. In many cases of acute inflammation the irritant persists in a milder form, and hence the proliferation of the connective tissue cells continues. Thus acute meningitis may be followed by chronic meningitis, acute nephritis by chronic nephritis, and acute endocarditis by chronic endocarditis. In such cases it may be impossible to draw a line between what is called chronic inflammation and the process of repair. The fibrinous exudate in pleurisy, for example, undergoes organisation essentially as a process of repair, yet the fibrous tissue which is produced is often taken as a sign of chronic pleurisy. So also in acute pneumonia, the fibrin in the air-vesicles instead of becoming absorbed in the usual way, may become organised, and the resulting fibrosis is spoken of as chronic interstitial pneumonia. On the other hand, the irritant may be of mild nature from the first, and never lead to the various phenomena of acute inflammation with its associated symptoms. It is thus important to distinguish from a practical point of view these two main types, viz. (1) chronic inflammation which is a sequel to acute, and (2) chronic inflammation which is of slow progress throughout, that is, chronic from the outset. The pathologist has constantly to determine to which of these varieties the chronic inflammation belongs.

As causes of *primarily chronic inflammation* there are many mild irritants of different kinds. They belong to three main classes, described as follows :—

(*a*) The irritant may be of *organismal* nature. Several kinds of organisms, of which the tubercle bacillus and the spirochæte of syphilis are the most important examples, are relatively slow in their action on the tissues, so that the lesions produced by them are chiefly proliferative in nature, corresponding to those which are seen in granulation tissue, and are accordingly spoken of as *infective granulomata.* Such organisms, of course, act by means of toxins, and these may spread widely and produce connective tissue overgrowth at some distance from the organisms. Thus, both in tuberculosis and in syphilis, diffuse fibrosis is a common result, in addition to the more cellular lesions which are produced around the organisms. The infective granulomata are typical examples of chronic inflammatory processes, and will be described later.

(*b*) The irritant may be of the nature of a mild *poison in solution* —either a toxin or a definite chemical substance. Cirrhosis of the liver, for instance, can be readily produced by poisons of various kinds, as will be described later. Lead is a good example of a metallic poison which both damages specialised cells and brings about connective tissue overgrowth.

(*c*) The irritant may be of a *particulate* or granular character; for example, when dust is inhaled for a long time, it comes to be absorbed into the lymphatic spaces of the lung, and gives rise to an overgrowth of connective tissue, that is, a chronic interstitial pneumonia. The formation of fibrous tissue around deposits in the tissues, e.g. lime salts, pigments, etc., and the encapsulation of dead material, are of similar nature.

HISTOLOGICAL CHARACTERS. Chronic inflammation is characterised, as has been stated, by overgrowth of the interstitial connective tissue, and this varies greatly in character. In the earlier stages it may be comparatively cellular, the cells spindle-shaped, and the connective tissue fibres delicate and scanty ; this is well seen in congenital syphilitic cirrhosis of the liver. On the other hand, in the later stages or where the process has been of very slow nature throughout, the chief change is a thickening of collagenous fibres, whilst cells are relatively scanty (Fig. 50). The vascularity of the new tissues also varies greatly. There is sometimes a considerable formation of new blood vessels and the interstitial tissue may appear of a reddish colour, as is often seen in cirrhosis of the liver and kidney. Very frequently, however, the tissue is relatively non-vascular, and this is specially the case when the interstitial growth is dense and fibrous and contains comparatively few cells. The wandering cells present are chiefly of the non-granular type—macrophages, plasma cells and lymphocytes, the last often predominating in very chronic cases, where they frequently occur in clumps between the dense fibres. In certain conditions, eosinophiles may be present in considerable numbers and even a small proportion of ordinary polymorpho-nuclear leucocytes may be met with. When the irritant is of particulate character or a substance difficult of absorption, the occurrence of foreign-body giant-cells (Fig. 48) is often a prominent feature, and when degenerative changes are going on in the neighbourhood, the macrophages may contain droplets of fat or other material. Cells filled with globules of myelin fat—the so-called foamy cells—are

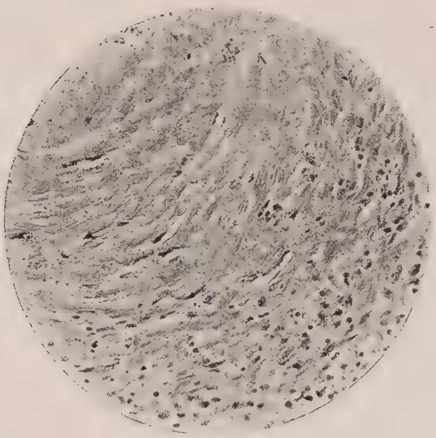

Fig. 50.—Chronic Inflammatory Nodule in Silicosis.

At the periphery fibro-cellular tissue is present, while towards the centre the collagenous fibres are thick and somewhat hyaline ; some stone particles are present between the fibres. × 125.

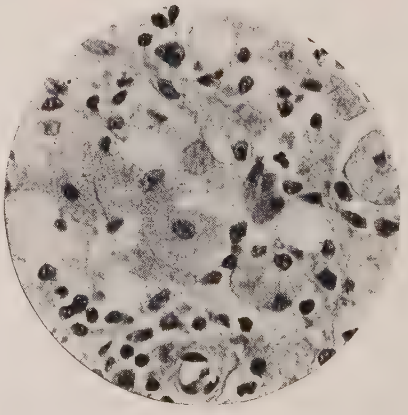

Fig. 51.—Foamy Cells in chronic Inflammation, showing the reticulated Character of their Protoplasm due to Myelin Fat. × 500.

of not infrequent occurrence (Fig. 51). Variations in the structural features of the new tissue formed as a reactive process, are well illustrated in the case of the infective granulomata, as will be described below.

Results. These are brought about mainly by the tendency of the newly formed tissue to contract. Serious effects may follow from the narrowing of orifices and tubes thus caused—for example, stenosis of the mitral valve in chronic endocarditis, stenosis of the larynx in syphilitic disease, etc. For this reason also, organs which are the seat of interstitial change tend to diminish in size, and, as the fibrous tissue is usually uneven in its distribution, irregularities on the surface result, often evidenced by a fine or a coarse granularity. Chronic inflammation in organs is usually attended to a greater or less extent by a loss of the special cells of the organ, i.e. a diminution of the parenchyma, and the relation of the two processes has been variously interpreted. A view formerly held was that the special cells were pressed upon by the fibrous tissue and underwent atrophy, but this can no longer be maintained. The directly opposite view has been put forward, viz. that the connective tissue growth is secondary to the damage done to the cells of the organ by toxins or other agencies. Such a view, however, is too restricted, as we know that the overgrowth of connective tissue in response to irritation takes place where there are no specialised cells at all. It appears to us that a toxic agent will have different effects on the two kinds of cells; thus it will lead to damage and disappearance of the specialised cells, and to a reactive overgrowth of the more resistant connective tissue cells. This is well illustrated in cirrhosis of the liver and in the cerebral lesions in general paralysis of the insane.

Other Causes of Fibrosis. Whilst fibrosis is a common feature of, and is usually due to, chronic inflammation, it must be recognised that it may be produced in other ways. For example, when the arterial blood supply to a part is diminished, atrophy of the specialised cells may occur, and this may be accompanied by an overgrowth of the supporting tissue. Thus, in the brain, patches of neuroglial overgrowth from which the nervous elements have disappeared, are common in arterial disease, and patches of fibrosis are frequently met with in the heart wall and in the kidneys, as a result of narrowing of the arterial branches. We may thus speak of a *replacement fibrosis*. In certain instances, however, the connective tissue formed has a supporting or defensive function, as is well exemplified in the case of the vascular system. The hypertrophy of the elastic and muscular tissues of the walls of arteries, which is met with in cases of long-continued high blood pressure, is often followed by degeneration of these elements, and their place is taken by overgrowth of connective tissue which acts as a support. When the media of the aorta is injured and weakened by syphilitic lesion, the intima corresponding to the site undergoes fibrous thickening, and this action is of a protective or compensatory nature. Accordingly, increase of connective tissue, in addition to being the result of chronic inflammation, may be of the nature of a *replacement* or may have a *supporting function.* The term *fibrosis* is best applied to these non-inflammatory varieties.

INFECTIVE GRANULOMATA

Tuberculosis. When a few tubercle bacilli gain a foothold in a tissue, a focus of reaction occurs, resulting in the formation of what is known as a *tubercle follicle.* At a very early stage the centre of the focus consists of a collection of swollen cells, often called 'epithelioid' or 'endothelioid,' whilst around them there is a zone of round cells, chiefly lymphocytes (Fig. 52). The endothelioid cells are usually oval, spindle-shaped, or irregular in form, have fairly abundant protoplasm and a faintly staining nucleus. Very soon, however, there is evidence of the action of the bacilli in producing damage to the cells. The central cells become swollen and lose their outline, their nuclei cease to stain, and ultimately they become fused into a homogeneous or slightly granular, structureless material. This is an example of Weigert's coagulative necrosis (p. 129), and sometimes a certain amount of fibrinous exudate is added to the necrotic material; the ultimate result is a necrotic centre surrounded by endothelioid cells, and these again by small round cells. Another common constituent of the tubercle follicle is the giant-cell, which occurs amongst

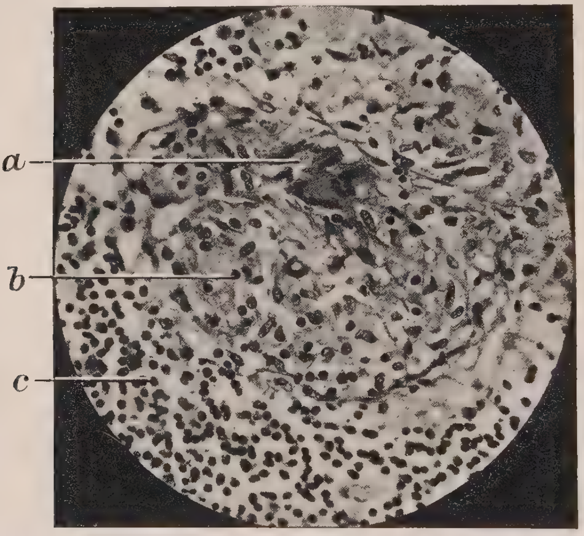

FIG. 52.—Tubercle Follicle at early stage.

(*a*) giant-cell in process of formation, apparently by fusion; (*b*) endothelioid cells; (*c*) lymphocytes. (Dr. J. W. S. Blacklock.) × 250.

the endothelioid cells. It is a large cell with somewhat irregular outline, and contains numerous oval or rounded nuclei resembling those of the endothelioid cells (Fig. 53). The nuclei are often arranged at the periphery, while the centre part of the cell may show signs of degeneration, being granular or hyaline in appearance. Or, again, the nuclei may be arranged in one or more clumps. The typical follicle is sometimes described as containing a central giant-cell surrounded by a zone of endothelioid cells, and those again by a zone of round cells. Such a structure is often met with, but the appearance is sometimes due to the fact that the section has not passed through the centre of the follicle, so that the central necrosed part is not seen.

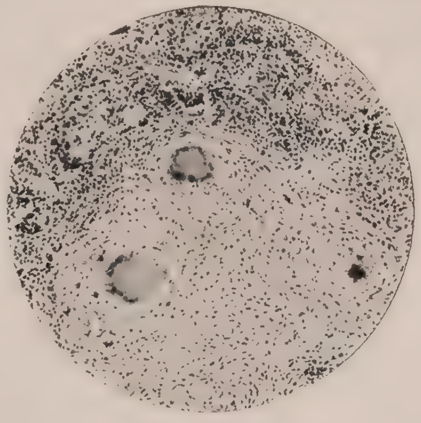

FIG. 53.—Tubercle Nodule more fully formed with three Giant-cells.

Note abundant infiltration of lymphocytes around. × 80.

The description which we have given applies to the commonest type of tubercle formation, but considerable variations may be met with. In the spleen and in the kidney, for example, the chief effect is often a rapid necrosis and caseation, whilst cellular proliferation occurs later at the periphery. Tubercle nodules are non-vascular in their substance, though considerable vascularity may be present at their margin, especially in those of chronic nature; and formerly it was believed by some that the central necrosis was due to a want of blood supply. We know now, however, that it is the result of the direct action of the tubercle toxins on the cells, and that the toxic action produces also the non-vascularity, as it leads to necrosis of the capillary walls and thrombosis. The occurrence of caseation in varying degree in the centre of the follicle is the rule; but in certain chronic conditions, for example in lupus, it may be slight or absent.

There has been considerable dispute as to the origin of the endothelioid cells, but we consider that they are mainly derived from the fixed cells of the part—the tissue histiocytes and also, though less frequently, fibrocytes. When a tubercle starts in a small vessel, as is often the case, the endothelial cells enlarge, actively divide and constitute most of the cells present—this at least is seen in the case of the Kupffer cells of the hepatic capillaries. Some writers favour the view that the endothelioid cells are derived chiefly from non-granular leucocytes, but we do not think that this is the ordinary mode of formation, though such leucocytes may be incorporated in the follicle. The giant-cells are formed from endothelioid cells, but there is difference of opinion regarding the process. Some consider that they are formed by amitotic division of the nuclei, while the cell protoplasm does not divide, but simply increases in amount. Others again hold that they are formed by a fusion of endothelioid cells, and this is supported by observations on the formation of giant-cells in tissue cultures. We think that the former view is the correct one in the majority of instances, though fusion of cells also occurs (Fig. 52). They may be regarded as a variety of foreign-body giant-cells (p. 87).

While the initial reaction conforms generally to the description given above, the ultimate results vary greatly, and thus tuberculous lesions come to present very different characters. We shall give some examples of these.

(*a*) *Acute Miliary Tuberculosis.* Sometimes there occurs an eruption of small tubercle nodules throughout the organs—an acute miliary tuberculosis. These nodules may be nearly all of the same character and therefore of the same age, and thus are due to an extensive dissemination of bacilli about the same time. This may occur in various ways. A tuberculous focus may implicate, or actually form in, the wall of a vessel, usually a pulmonary vein, and then ulcerate into it, leading to a discharge of bacilli into the circulation. For example, one may sometimes find a caseous bronchial gland which has thus eaten into a pulmonary vessel. Again, in children, where there is extensive caseation of the broncho-tracheal glands passage of bacilli into the venous system readily occurs. In some cases tubercle spreads from the abdominal lymphatic glands to the thoracic duct; tubercles form in its wall, and then undergo softening and ulceration. From such lesions bacilli may be carried up the duct and thus reach the veins.

There is no justification for the supposition that acute miliary tuberculosis represents either a special virulence of the bacilli or a specially low resistance on the part of the patient; it is merely the result of what may be regarded as an accidental entrance of bacilli to the circulation in large numbers.

(*b*) *Caseous Lesions.* Frequently the necrotic action of the bacilli is most in evidence and thus large areas of caseation result, these being surrounded by a connective tissue in which giant-cell systems are usually to be found (Fig. 54). Large caseous masses are specially common in lymphatic glands, and often occur in the kidneys, epididymis, supra-renals, etc. The caseous material may have a firm consistence, as in the tuberculous masses in the brain, though frequently it is pulpy or even semi-fluid. In the case of chronic tubercle of bones, notably the vertebræ, the caseous material has a tendency to become softened; it attracts chemotactically polymorpho-nuclear leucocytes, and becomes a caseous pus. This increases in amount and burrows along muscles, as occurs in lumbar and psoas abscesses; owing to the absence of the signs of acute inflammation, these are known as *cold abscesses.*

(*c*) *Tuberculous Granulation Tissue.* Again, tubercle may lead to the formation of abundant granulation tissue. This is a noteworthy feature of tuberculosis of the joints, where the synovial membrane becomes covered with a layer of pinkish and somewhat gelatinous granulation tissue. Here again the tubercles become obscured by the newly formed tissue, but giant-cell systems are to be found in it on microscopic examination.

(*d*) *Fibrotic Lesions.* The growth of tubercles may be very slow and localised, and much fibrous tissue may form around them, fibroid tubercles thus resulting. In the lungs, in connection with these, there is often a considerable spread of fibrous tissue into the parts beyond, apparently due to the diffusion of toxic products along the lymphatics. The lesion thus comes to be one of chronic interstitial pneumonia, and its real nature may not be apparent on naked-eye examination.

(*e*) *More Acute Inflammatory Changes.* Tubercles, when abundant, may give rise to fibrinous exudation. This is well illustrated in the case of tuberculous meningitis, where there is a growth of tubercles along the lines of the arterial branches, which is followed by exudation into the subarachnoid meshwork around. In such cases, polymorpho-nuclear leucocytes, many of them degenerated, may be found along with lymphocytes, etc., both in the meninges and in the cerebrospinal fluid obtained by lumbar puncture. Tuberculosis of serous cavities also is often attended by fibrinous and serous exudates, and in the case of the pericardium the exudate may be hæmorrhagic in type (p. 371). When the exudate is serous the cells are chiefly lymphocytes.

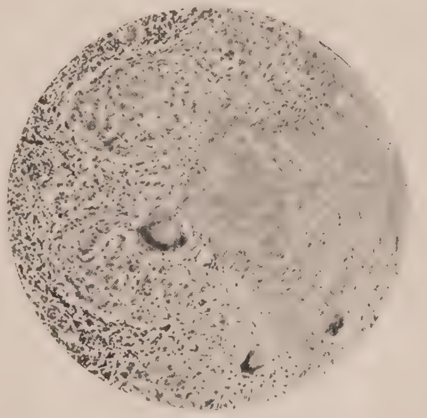

FIG. 54.—Tuberculous Lesion with Caseation.

On the left side, there is cellular tissue with tubercle follicles and giant-cells; on the right, caseation and loss of nuclear structure. × 80.

(*f*) *Tuberculous Ulcers.* When tubercle follicles form in a mucous membrane, as often occurs by direct infection from the surface, ulceration is apt to follow. Such ulcers, small at first, tend to spread and are apt to be intractable. They are common in the intestine, larynx, bronchi, bladder, etc.

The diversity of tuberculous lesions may be partly explained by varying degrees of resistance or relative immunity of the tissues, and it may be said in a general way that the formation of tubercles and connective tissue proliferation indicate a *relative immunity*, whilst gn:?.

diffuse caseation and exudative processes occur in the converse condition. The number and virulence of the bacilli will of course also play a part. A comparison of the pulmonary tuberculous lesions in the young child and in the adult shows that the latter has acquired a certain degree of immunity. We may say that infection in the earliest years of life, which is usually by the respiratory passages, is of very common occurrence. It may lead to a fatal result, as will be described later (p. 416), or may undergo healing, which leads to a varying degree of immunity. There then follows up till puberty a period when caseating lesions are met with in internal organs, such as brain, adrenals, genito-urinary system, as well as in bones and lymphatic glands. This is sometimes spoken of as the *metastasising* period. In adults the outstanding lesion (apart from the sequelæ of the previous) is pulmonary tubercle, which is usually the result of reinfection. It is often of a chronic nature and often undergoes healing. This, however, is only a general statement. Miliary tuberculosis is in a sense an accidental phenomenon which may occur at any period, though it is commonest in the early years of life. To what extent the diversity of lesions at different periods depends on tissue allergy (p. 194) resulting from infection, must be regarded as still an open question.

Syphilis. The lesions of syphilis show remarkable variety in their character and distribution; in fact one may say that no other disease is more protean in its manifestations. But while this is so, it is found that the reaction of the tissues to the causal agent—the *Spirochæta pallida* or *Treponema pallidum*—is pretty much the same at all stages. The organism may be regarded as a slowly acting irritant, and the response is chiefly on the part of the non-granular leucocytes and connective tissue cells, there being as a rule practically no chemotactic effect on the polymorpho-nuclear leucocytes. In certain cases masses of cellular granulation tissue are formed; hence the disease is classed among the infective granulomata. But syphilis is peculiar in having also the characters of a protracted specific fever or exanthem, with distinct incubation period, primary lesion, and febrile period with skin eruption. If we except congenital syphilis, we may say that the disease is the result of direct inoculation of skin or a mucous surface covered by squamous epithelium, and usually, if not always, through some crack or abrasion. The predilection of the organism for squamous epithelium is shown by the site of the primary lesion in the human subject, and is emphasised by experiment on apes, as it is found that with a few special exceptions, e.g. intratesticular inoculation, the disease can be successfully transmitted only by scarification of such an epithelial surface. It would appear almost as if something resident in the epithelial cells were necessary for the maintenance of the organisms at first; subcutaneous inoculation in apes, for example, fails to produce the disease.

The COURSE OF SYPHILIS is usually divided into three stages, and these essentially depend upon the distribution of the spirochætes.

The first manifestation, or *primary stage*, appears after a period of incubation of usually from three to four weeks, in the form of the primary sore or chancre. This represents the local reaction in the subepithelial connective tissues, and is associated with induration of the related lymphatic vessels and glands, due to the spread of the organisms. The primary lesion eventually becomes resolved.

In the *secondary stage*, which usually appears from two to three months after infection, considerable variations occurring, the organisms gain access to the blood stream, and though they are never numerous there, they become distributed throughout the body. They settle especially in the skin and mucous membranes covered by squamous epithelium, producing in the former various skin eruptions, and in the latter mucous patches and catarrh, e.g. of the fauces. In relation to the wide dissemination of the spirochætes there is a general enlargement of lymph glands, though some groups may be specially affected. Owing to the manner of distribution, the lesions in the secondary stage are multiple and symmetrical. In course of time these superficial lesions undergo retrogression, and may leave no result, while the organisms disappear from the secretions of infected parts. The onset of these signs of the secondary stage is attended by malaise, anæmia and pyrexia, in varying degree. While dissemination of the spirochætes by the blood is essentially a feature of the secondary stage, it is of importance to note that they may be present in the blood at a much earlier stage. In fact there are cases on record where syphilis has been accidentally transmitted by transfusion of blood at a time before the primary lesion has appeared in the donor of the blood. (McCluskie.)

In the *tertiary stage*, the general distribution and action of the spirochætes have come to an end, and the organisms become localised in an irregular manner, especially in the internal organs. The lesions accordingly are asymmetrical and less numerous, but they are also larger and lead to important results of a permanent nature. They are chiefly of the nature of granulation tissue masses or *gummata*, which undergo necrosis, and *chronic interstitial inflammation*; while arterial disease, which may begin in the secondary stage, now becomes a marked feature. Lesions of the tertiary type may appear within the first year, but are commoner in the second or third year: they may occur also much later. Gummata often become absorbed in the natural course of the disease, cicatrices resulting.

Such is the usual history of syphilis, when its course has not been modified or cut short by treatment, and of course the severity of the symptoms and lesions varies much in different cases. But in a certain small proportion of cases there occur at a much later period two important nervous diseases, viz. locomotor ataxia, and general paralysis (pp. 758, 767). The lesions in these appear at first sight to be of a different order, and were supposed to be the late expression of some damage to the nervous system during the actual disease; hence they were often spoken of as 'parasyphilitic' in nature. It is now known, however, that they are due to the presence of the parasites in the central nervous system.

STRUCTURAL CHANGES. The *primary sore* appears as a papular thickening of dull reddish tint, and as it increases in size, induration becomes more and more marked till it may assume a cartilage-like hardness. The epithelium over it may be partly lost, and there may be a varying amount of exudate which, in the case of a skin lesion, is usually scanty and forms a crust. Sometimes, however, especially when the lesion is on a mucous surface and the part is not kept clean, there may be a considerable amount of superficial necrosis and ulceration, and in such cases a great variety of organisms are present along with the spirochætes. On microscopic examination there is seen in a section through a fully formed chancre, a cellular granulation tissue extending close up to the base of the epithelium which shows swelling with irregularity, being at some places thickened, at others rather stretched. In the central parts the cells are diffusely arranged, but at the margin they form strands, especially along the vessels. The tissue is very vascular and the small vessels are often surrounded by a sheath of pale and rather swollen cells (Fig. 55). Proliferation of the intimal cells and blocking of the lumen may be seen in the minute vessels, while larger twigs show endarteritis and periarteritis (Fig. 56). The interstices of the tissues are packed with round cells—lymphocytes, plasma cells and mononuclear leucocytes—the large proportion of plasma cells

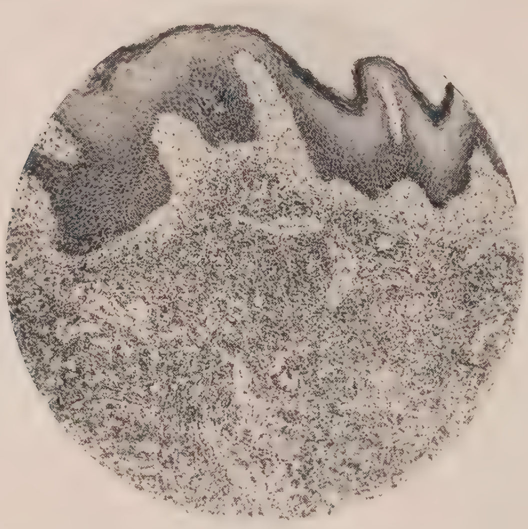

FIG. 55.—Section of primary chancre showing extensive infiltration of *cutis vera* with lymphocytes and plasma cells and some newly formed blood vessels. × 60.

being often a striking feature. Almost no polymorpho-nuclear leucocytes are present except in the superficial parts when there is ulceration. Proliferation of the connective tissue cells and thickening of the stroma take place and increase the induration; but the hard character in the earlier stages is due chiefly to packing of the connective tissue spaces with cells. After a time the reactive changes come to an end, the cells gradually become absorbed, and only a certain amount of thickening of the fibrous reticulum remains. As a rule there is left little or no cicatrix visible to the naked eye, but there may be a distinct scar if there has been much ulceration. The histological changes along the indurated lymphatics are essentially of the same nature. In the primary chancre there is no necrosis or caseation, and the lesion differs from tubercle also in the absence of any focal character. Giant-cells are rarely met with (Fig. 57); if present, they are relatively small. Spirochætes are abundant in the primary sore and usually can be readily found by microscopic examination with dark-ground illumination of the serous fluid obtained from the surface by applying a mild irritant such as alcohol.

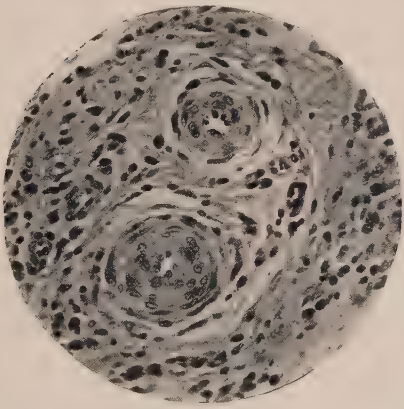

FIG. 56.—Section of Chancre at late stage, showing Obliterative Changes in two Arterioles and Advancing Fibrosis around. (D. F. C.) × about 200.

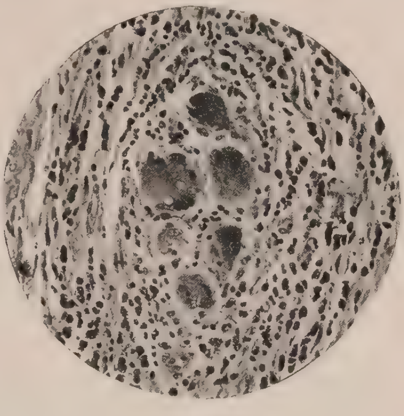

FIG. 57.—Section of Chancre, showing Clump of Giant-cells surrounded by Plasma Cells, Lymphocytes, etc.

Note that there is no follicle formation such as is seen in tubercle. D. F. C). × about 170.

The lesions in the *skin* and *mucous membranes* in the secondary stage are essentially small areas of reaction around the spirochætes, distributed by the blood stream as described. The primary change is in the sub-epithelial connective tissue, and here again we find vascular engorgement and round-cell infiltration, the large number of plasma cells being a prominent feature. Various nutritional changes occur in the epithelium, and on these the characters of the eruption in part depend, scaliness being a common feature. Cellular infiltration occurs also around and into the hair follicles; the nutrition of the hairs is then interfered with and they may fall out. The ordinary course is for all these disseminated lesions of the skin and mucous membranes to undergo retrogression and to disappear.

The *gumma* of the tertiary stage is a cellular granulation tissue mass, which at first may present a pale pinkish and somewhat translucent appearance, but the central parts soon undergo necrosis, and accordingly it usually consists of yellowish and necrotic material, surrounded by fibrous tissue. In course of time gummata have a great tendency to undergo absorption and shrinking, and thus cicatricial areas are a common result. In addition, chronic interstitial inflammation or fibrosis, often of a spreading character, is a common lesion, sometimes associated with distinct gummata, sometimes apart from them; and this chronic inflammation may be attended at places by necrosis or gummatous change. Structurally a gumma resembles closely the primary sore, but differs in the occurrence of necrosis at an early period (Fig. 58). This may be due in part to the obliterative changes in the blood vessels, and possibly in part to the direct action of the spirochætes, although these are only in small number. But such an explanation is unsatisfactory and it seems more justifiable to regard the necrosis as being chiefly due to an increased tissue sensitiveness or allergy developed in the course of the infection. In the necrotic areas the structural outlines may be preserved for a considerable time, the cells not having the same tendency to fuse into amorphous material as is seen in tubercle. Giant-cells may be present in the granulation tissue at the periphery, but they are usually smaller than in tubercle, and there is an absence of concentric formation of endothelioid cells around them, resulting in follicles. Nevertheless the microscopic diagnosis between the two diseases may be a matter of difficulty, chiefly owing to the fact that tubercle may sometimes occur without its characteristic features. The important *vascular lesions* of syphilis are described below, but here it may be stated that those in the larger arteries are due to the lodging of the spirochætes in the adventitial sheath, whence they extend into the media. They give rise to cellular

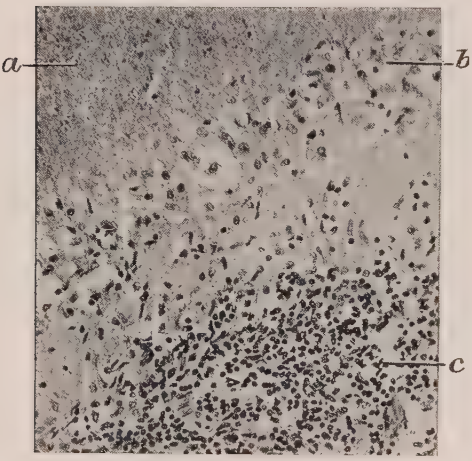

FIG. 58.—Portion of Gumma.

(*a*) Necrotic area with granules of chromatin. (*b*) Zone of connective tissue growth. (*c*) Infiltration with plasma cells and lymphocytes. × 200.

infiltrations in these coats, of nature similar to those described, and sometimes even some necrosis may follow (p. 301).

In *congenital syphilis* the lesions are of the same type of reaction, but present special features, chiefly as the result of the large numbers of spirochætes which are often present. Thus diffuse proliferations of connective tissue cells occur in liver, lungs, pancreas, etc., and there may be also minute foci of more intense reaction followed by necrosis—the so-called miliary gummata. Such lesions may occur throughout the affected organs and lead to death at an early period, or they may be more localised and followed by fibrotic change; they will be described in connection with the various organs.

Actinomycosis. This disease is produced by organisms of the streptothrix class, which occur in the form of small rounded colonies with radiate arrangement at the periphery—hence the term 'ray-fungus.' More than one species of streptothrix may produce the disease, and there are also species which grow in a more diffuse manner and cause somewhat similar lesions. In the bovine species, in which actinomycosis is common, the lesions are localised and are of the nature of large granulomatous masses which occur especially in the tongue and in connection with the jaw. In the human subject, however, they are more of a suppurative type. The parasite as a rule gains entrance by the alimentary tract, and the lesions usually occur either in the region of the mouth or in connection with the intestine, especially the colon (p. 568). Sometimes in the lesions about the face, there is much formation of granulation tissue, in which small foci of suppurative softening containing the parasites are present ; but elsewhere chronic suppuration is the outstanding feature, and when a pyæmic condition develops, as is not uncommon, secondary abscesses form in the liver and other organs. The abscesses have often a loculated character (Fig. 383).

Leprosy. In leprosy, which is produced by an acid-fast bacillus resembling in many respects the tubercle bacillus, we have an excellent example of a granulomatous type of lesion. The bacilli lead to the formation of collections of cellular granulation tissue which occurs in small masses and as a diffuse infiltration ; these lesions appear especially in the skin of the face, where they lead to irregular thickening and distortion of the features. They occur also in the skin of other parts, in mucous membranes and, to a certain extent, in internal organs. Such lesions form the characteristic feature of the common nodular or tubercular type of leprosy. In the granulation tissue, which may remain for a long time in a comparatively cellular condition, the great majority of the cells are of a rounded form, and correspond in appearance and size with mononuclear leucocytes. Some of the cells may be considerably larger, and may contain a convoluted nucleus or multiple nuclei, but the giant-cells such as are common in tuberculosis do not occur. Amongst the cells are connective tissue fibrils, and the tissue is comparatively vascular. The cells contain the bacilli in large numbers and may be practically packed with them. Leprous lesions, as contrasted with tuberculosis, are further characterised by the absence of focal arrangement of the cells resulting in the formation of follicles, and by the non-occurrence of necrosis and caseation. At a later period, fibrosis and shrinking of the granulation tissue may take place. In another type of leprosy, the anæsthetic form, the chief change is a chronic interstitial neuritis, which is produced by invasion of the sheaths of the nerves by the bacilli. In this type, however, the bacilli occur in much smaller numbers. There is less formation of cellular tissue, while thickening of the fibrous tissue, with destruction of the nerve fibres, is the main feature.

Glanders. This disease occurs naturally amongst equines, but occasionally it is transferred to the human subject. In the *horse*, for instance, it is characterised by the formation of inflammatory thickenings and nodules in the septum nasi and upper respiratory passages, these giving rise to irritative discharge and tending to ulcerate. Nodules may be formed also in the internal organs, notably in the lungs. They have a pale greyish or yellowish centre, sometimes softened, and a congested periphery; they may reach the size of peas or be even larger. The central parts of the lesions may be said to show a process of imperfect suppuration, and a prominent feature is the large amount of nuclear detritus formed by karyorrhexis of the polymorphonuclears. At the margins the changes are mainly proliferative. Infection in the horse occurs also through the skin surface and a corresponding lymphangitis and inflammatory enlargement of the lymphatic glands result, constituting the so-called farcy pipes and buds. In the glands there may be a considerable amount of suppurative softening. The disease is rare in the *human subject* and occurs chiefly by direct inoculation of a scratch or abrasion by material containing the bacillus. Local inflammatory reaction and spreading lymphangitis occur but the lesions are more acute than in the horse, and not infrequently secondary lesions form in the skin, muscles and internal organs, and lead to a fatal result. The changes are of a suppurative rather than a granulomatous type and there is often admixture of blood in the pus. Sometimes the disease is more chronic in character, the local lesion becoming an irregular ulcer with thickened margins; in this case also metastatic suppurations may occur. The reaction produced in the horse by the glanders bacillus has been aptly described as intermediate in type between tuberculosis and suppuration, and it will be seen from the account given that in the human subject it tends still more to the suppurative type.

Other Granulomata. In addition to the diseases mentioned there are a considerable number of infections characterised by granulomatous lesions and caused by parasites of different kinds—bacteria, higher fungi and even protozoa. The diagnosis of these infections as a rule rests on the identification of the parasite concerned. Some of these may be briefly mentioned.

Rhinoscleroma is a granulomatous infection of the nose, pharynx and larynx, nodular thickenings growing in these parts. The lesions are essentially granulomatous and in them there are numerous round cells, the protoplasm of which contains a gelatinous material in droplets which may fill the whole cell and push the nucleus to the side. Within these cells a bacillus resembling Friedländer's pneumobacillus is present in considerable numbers. The disease is not uncommon in some countries on the Continent but is rarely met with in this country. *Aspergillosis*, produced by an ascomycete (*Aspergillus fumigatus*), is met with in the lungs in the form of a chronic infection leading to the formation of nodules, which undergo necrosis resulting in cavity formation. *Blastomycosis* includes a number of infections caused by different species of saccharomycetes. The lesions are most frequent in the skin and are characterised by the formation of granulomatous tissue in which endothelioid cells and giant-cells are often prominent features. In some cases the lungs are affected and the condition may resemble tuberculosis. The presence of the yeast-like organisms in the lungs can be easily detected as a rule. *Sporotrichosis* is caused by a hyphomycete, the *Sporotrichon beurmanni*. It too affects chiefly the skin, in which diffuse granulomatous tissue forms, which, however, is accompanied by a tendency to suppuration and the formation of small abscesses. Occasionally lesions occur in the internal organs. In *Delhi sore* or *tropical ulcer* we have an example of ulcerating or granulomatous lesion produced by a protozoon, the *Leishmania tropica.*

Lymphogranuloma inguinale. This is a granulomatous venereal infection in which the chief lesions are in the lymphatic glands ; it is sometimes known as the 'fourth venereal disease.' It is not uncommon in America, occurring chiefly in negroes though not confined to them. The primary lesion is slight and often escapes notice. Swelling of the inguinal lymphatic glands becomes distinct from fifteen days to three weeks after exposure to infection and is accompanied by systemic disturbance. The swellings become firm and tender and the skin over them assumes a reddish-violet tint. Adhesion of the glands to the skin then occurs, the glands soften in the centre and multiple fistulous openings form. In the female, owing to the lymph drainage of the vulva being towards the pelvis, the lesions are mainly in the latter and serious complications often follow. These include stricture of the rectum, formation of fistulæ and occasionally a condition of external elephantiasis. The disease has been shown to be due to a filter-passing virus and has been transmitted to apes and other animals. Frei showed that when pus from a bubo diluted with saline was inoculated intradermally in a patient suffering from the disease a distinct area of inflammatory redness developed at the site of inoculation. This reaction is specific and can be used in diagnosis ; it is known as Frei's reaction. The disease is known also as 'climatic bubo' or poradenitis.

Granuloma inguinale. This is another granulomatous disease, quite distinct from that just described ; it is not uncommon in America and appears to be practically confined to negroes. The lesions are in the cutaneous and subcutaneous tissues, and occur on and in the neighbourhood of the external genitals ; chronic ulceration often follows. The characteristic feature is the presence in the granulation tissue of macrophages containing numerous small oval organisms (these are often known as 'Donovan bodies,' a misleading term as they have no relation to Leishman-Donovan bodies). The organism is a pleomorphous bacterium which has been obtained in pure culture, and the disease has been reproduced by inoculation with cultures.

In addition to these examples, there are also some other diseases with multiple lesions which present characters somewhat intermediate between those of granulomata and true tumours. *Lymphadenoma* is one of these and will be considered later (p. 508). Another is *mycosis fungoides,* which is characterised by the formation of multiple nodules of considerable size in the skin, especially of the upper parts of the body, and often preceded by local erythematous patches. The nodules are at first of cellular character and a great variety of cells are present—lymphocytes and plasma cells, macrophages, multinucleated giant-cells, etc. The lesions, on the whole, are of the granulomatous type, but no organisms have been found and the etiology is unknown.

REPAIR

Among the lower orders of the animal kingdom, when a part of the body has been removed or destroyed by injury, a remarkable regeneration of the lost structure often occurs and complete restoration may follow. In the higher vertebrates, however, regeneration in the strict sense is met with only in a rudimentary form, and any breach of continuity or gap is repaired mainly by the formation of a new tissue in which specialised structures are not restored to any extent ; and, furthermore, whilst various specialised cells have a certain power of proliferation when they are injured, this process takes place slowly and to a slight degree, as compared with the growth of the interstitial tissue. Accordingly, repair of organs or specialised tissue is effected chiefly by connective tissue. If, however, damage is inflicted on the specialised cells alone, as in toxic necrosis of kidney and liver cells, it may be repaired by proliferation of surviving specialised cells and a complete restoration may be effected. The covering epithelia of skin and mucous membranes have, like connective tissues, great reparative capacities.

As has been already described, the essential factor in bringing about reparative proliferation is breach of continuity, and proliferation thus set up will go on indefinitely or until continuity is restored. The primary object in the process is a filling up of the gap by a cellular tissue, and this is effected mainly by the growth of connective tissue cells or fibroblasts along with numerous newly formed blood vessels. So far as the connective tissue cells are concerned the process is a comparatively simple one. Resting fibrocytes become enlarged, oval or spindle-shaped with processes, and come to acquire the characters of fibroblasts (Fig. 32). The fibroblasts have a characteristic appearance, and we believe that ordinarily they are the only cells which take part in the production of new fibrous tissue. The possibility of other cells being concerned has already been discussed (p. 83). Their energies are at first chiefly devoted to proliferation by mitosis, but after the breach has been occupied, the formation of collagen fibrils follows, and as this goes on the cells gradually become reduced in size and ultimately assume again the characters of adult connective tissue cells.

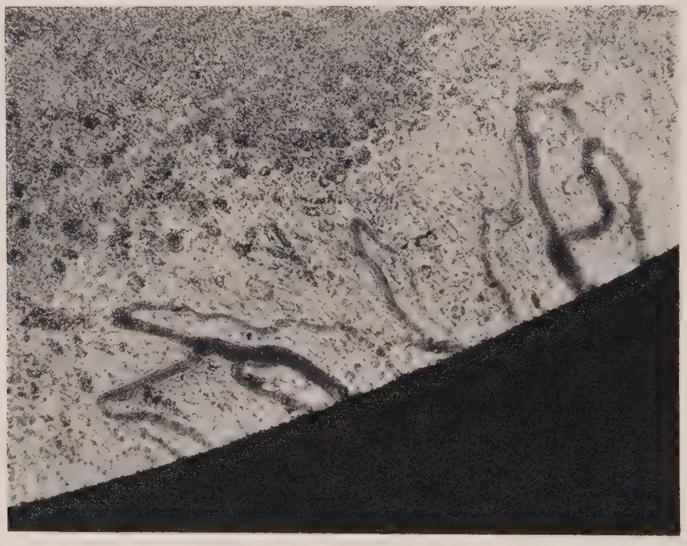

Fig. 59.—Capillary loops growing into thin blood clot, as seen in special chamber attached to rabbit's ear. (Photograph taken during life.) Note large numbers of macrophages in advance of growing vessels. (Prof. H. W. Florey.)

The formation of new blood vessels in every case takes place from the pre-existing vessels. According to Thoma, the first change is the formation of small projections from the capillary walls, which soon take the form of hollow endothelial buds, while from the end of a bud a delicate filiform process extends into the tissues. Such a process becomes united with another in the vicinity, which has grown out in a similar way from a capillary, and then the two corresponding hollow buds grow along the line of guidance thus formed and become confluent. In this way a new capillary loop has been formed and subsequent growth occurs by elongation of the loop. Such loops are formed in large numbers in relation to a wound, and grow into the breach (Figs. 59, 60, 64). They are accompanied by fibroblasts which are often arranged as a sort of sheath around them. Some of these newly formed vessels become of larger size and acquire a supporting wall of connective tissue. At a later stage, after the breach has been completely occupied by this vascular granulation tissue, many of the newly formed capillaries become closed and ultimately disappear. This process is called *devascularisation*. We shall now describe the process of healing more in detail, and afterwards consider the powers of repair possessed by different tissues.

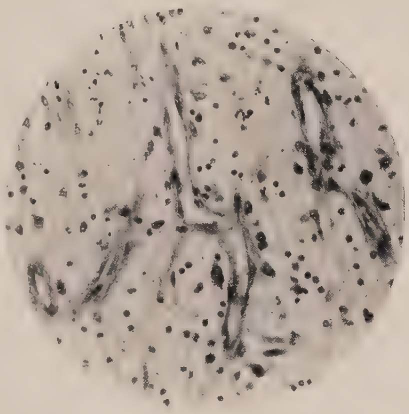

FIG. 60.—Newly formed Blood Vessels in granulating Wound, showing the characters of their Walls. (G. H. W.) × 200.

Healing of Wounds

(*A*) *Primary Union.* In the case of a simple incised wound such as is made in aseptic surgery, the process of healing is of simple nature, and takes place with comparative rapidity. After bleeding has been arrested, and the margins have been fixed in apposition, the adjacent surfaces become glued with a thin layer of coagulum. There is a slight degree of congestion of the superficial vessels with some exudation of lymph, but this is ordinarily of quite trifling degree; and only a few leucocytes emigrate from the vessels into the clot. Within a short time the connective tissue cells become swollen and divide by mitosis; and they then, in the form of fibroblasts, migrate into the thin layer of coagulum, which undergoes absorption by the action of these cells and of leucocytes. Capillary buds accompany the fibroblasts, but often little vascularisation is necessary. The fibroblasts from the adjacent sides become intermingled, they arrange themselves at right angles to the line of the wound, and produce collagen fibrils which bring about the permanent union. At the same time the epithelial cells have proliferated; they then grow over the line of incision from the two sides and restore the continuity of the epithelial covering. At the end of five or six days the process is practically completed, and only a narrow line of young connective tissue is present to mark the line of the incision (Fig. 62). If an irritating antiseptic has been used, there is more serum discharged from the vessels, and if the wound has been a large one the discharge may be considerable. In such a case the emigration of leucocytes continues a longer time, and the formation of fibroblasts and new capillaries is likewise of longer duration and more abundant. The ultimate result is that a more distinct line of fibrous tissue is left than in the case of simple aseptic healing (Fig. 63). The presence of pyogenic organisms in the wound may lead to inflammatory reaction, which may go on to suppurative softening of the coagulated lymph. Primary union then fails to occur, and the wound has to heal from below upwards by granulation.

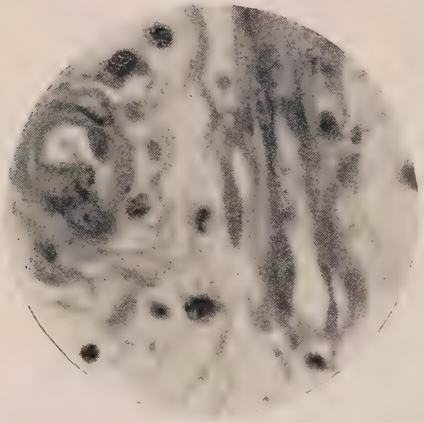

FIG. 61.—Higher-power View of newly formed Vessels. One is cut transversely, the other longitudinally; fibroblasts and leucocytes also present. (G. H. W.) × 600.

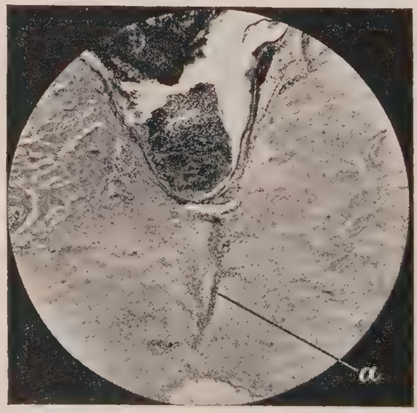

FIG. 62.—Aseptic Abdominal Wound with healing after five days.

The incision is represented merely by a vertical cellular line (*a*). The round body on the surface is a small scab. × 45.

(*B*) *Healing by Granulation.* The term granulation tissue was originally applied to the deep-red tissue of somewhat granular aspect, seen in the floor of a healing ulcer. Such tissue is comparatively cellular and very rich in young blood vessels, and the term is now applied to any newly formed tissue with these characters. The repair of a gap in the skin surface, however produced, or of a wound which has failed to unite by primary union, is effected by the growth of granulation tissue from the deeper parts. In the floor of the wound there is an active formation of new capillaries from the pre-existing blood vessels in the manner already described, and they grow upwards as vascular loops at right angles to the surface (Fig. 64); at their upper extremity they often have a coiled arrangement. Along with them there grow a large number of fibroblasts Fig, 65) which are at first mainly arranged parallel to the new capillaries. Active emigration of leucocytes, chiefly polymorpho-nuclear, takes place from the new capillaries, especially in their upper part, and these cells pass to the surface, where they play an important part in checking the growth of bacteria, and thus in allowing healing to progress. When there is little irritation from bacteria, the exudation is relatively small in amount and is rich in leucocytes—the so-called 'laudable pus.' On the other hand, excessive irritation from continued bacterial growth gives rise to a more abundant and more serous discharge; or there may even be a fibrinous exudate on the surface. Under these conditions the growth of the young vascular tissue may be checked and part of it may become destroyed; and the process of the healing will not be resumed satisfactorily until the bacteria have been overcome, and the source of irritation and damage has thus been removed. When granulation tissue has been formed, however, it usually acts as an efficient protec-

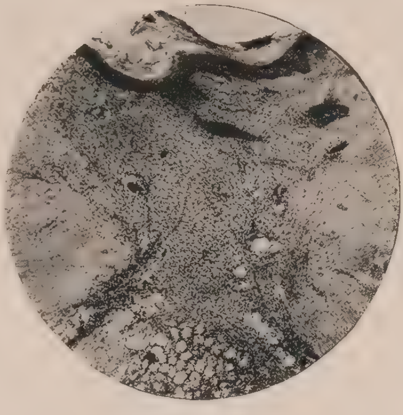

Fig. 63.—Healed Abdominal Wound.

There has been irritation and healing has been protracted. Note that the line of cellular tissue is much broader than in Fig. 83. × 30.

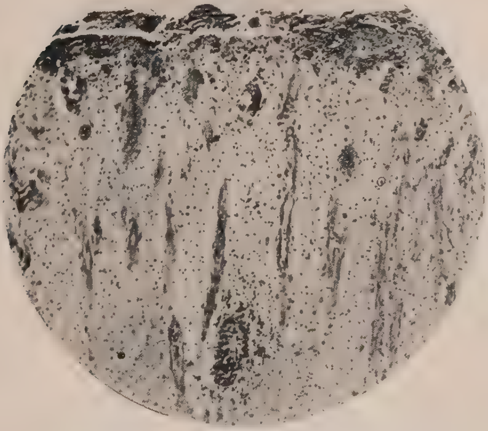

Fig. 64.—General View of Granulating Wound, showing the Vertical Lines of newly formed Blood Vessels. × 60.

tive layer which prevents absorption of toxins or penetration of bacteria into the underlying tissues.

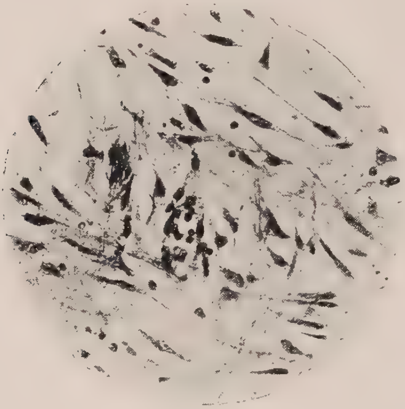

FIG. 65.—Fibroblasts in Healing Wound, showing the characteristic Shape and early Formation of Fibrils. × 250.

The growth of the vascular tissue is directed to filling up the gap, and when this process has gone on for some time, the fibroblasts in the deeper part arrange themselves more or less parallel to the surface, that is, at right angles to the vessels (Fig. 66), and collagen fibrils appear between them. How they are produced is not fully understood; what one sees is merely that delicate fibrils appear between the cells and then gradually increase in thickness. Formation of fibrous matrix then proceeds from below upwards. When the gap has been sufficiently filled up, the cells of the epithelium at the margin begin to proliferate and grow over the young vascular tissue. But this occurs satisfactorily only when bacterial growth has been properly restrained, chiefly by the action of the leucocytes. The first object of the epithelial cells is to cover in the surface as quickly as possible, and the growing epithelium is at first a thin layer of flattened cells (Fig. 67), through which leucocytes are sometimes seen to be still passing. It may be mentioned that when the tissue has become completely covered by epithelium, emigration of polymorpho-nuclear leucocytes usually stops, and these cells gradually disappear from the tissues, the leucocytes then present being chiefly mononuclear leucocytes, plasma cells and lymphocytes. The layer of epithelium thus formed then increases in depth, and the cells become differentiated into the superficial cells of the stratum corneum and the rounded cells of the stratum Malpighii (Fig. 68). When the young tissue has been covered by epithelium, the growth of blood vessels

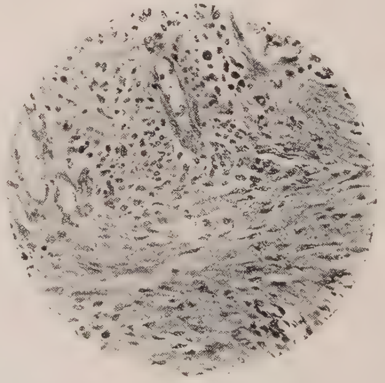

FIG. 66.—Deeper Part of Granulating Wound.

Below, the collagen fibrils are being formed parallel to the surface; above, the vessels are seen running in a vertical direction. (G. H. W.) × 150.

comes to an end, and a process of obliteration of the new vessels, or devascularisation, sets in. This is accompanied by the formation of abundant collagen fibres, and ultimately the tissue becomes dense and fibrous, and is comparatively avascular—the characteristic white scar tissue. The process of complete devascularisation and cicatrisation is a somewhat gradual one, and thus a considerable time elapses before the scar loses its reddish appearance. The newly formed epithelium covering the scar assumes the ordinary characters, but it is usually somewhat thinner than the normal epithelium, and the regular arrangement of the papilliform processes of the corium are wanting. Where the special structures of the skin—sweat glands, hairs, and sebaceous glands—have been completely destroyed, there is no regeneration of them in the scar. If, however, a portion, say of a sweat gland, has survived, a certain amount of repair may occur, but as a rule the cicatricial tissue is devoid of these structures.

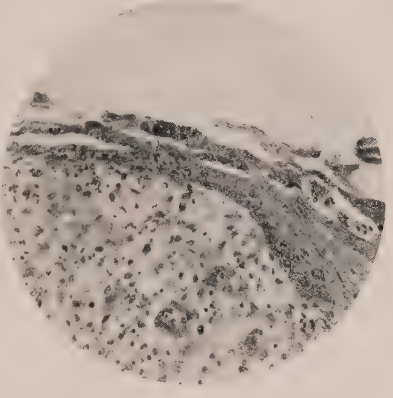

Fig. 67.—Granulating Wound with early Growth of Epithelium over the Surface.

The epithelium is growing from the right-hand side and tapers off as a thin layer. (G. H. W.) × 200.

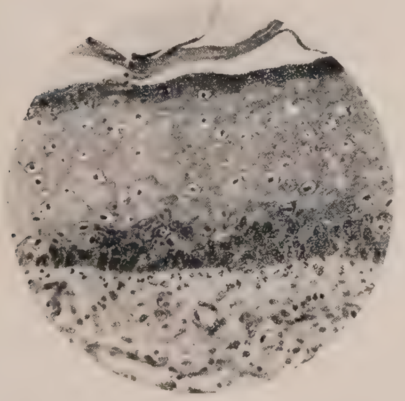

Fig. 68.—Newly formed Epithelium on Healed Ulcer.

The cells are in several layers but there is little differentiation, and there is no formation of papillæ. (G. H. W.) × 200.

The *repair of fractures of bone* occurs according to the same general principles as that of wounds of the soft tissues, but is more conveniently considered later in connection with diseases of bone (p 807). The account there given may, however, be suitably read by the student along with the foregoing.

Processes similar to those seen in repair occur in what is called *organisation*, that is, penetration of certain inert material, e.g. thrombus, fibrin masses, etc., by young connective tissue cells and young vessels. Granulation tissue is formed also around collections of pus so as to constitute an abscess wall, and is a prominent feature in chronic tuberculous lesions, e.g. around phthisical cavities and in tuberculosis of joints. In all such cases the processes concerned are essentially of the same nature, and the ultimate result is an increased formation of connective tissue which will of course present different appearances according to the stage.

The mode of *organisation of a thrombus* is of considerable interest and may be briefly sketched. When an artery is ligatured, a fairly firm thrombus forms on the proximal side and is of conical or tapering form ; that on the distal side is looser and more irregular. The presence of the thrombus leads to reactions on the part of the vascular endothelium, the connective tissue cells and the vasa vasorum. The endothelium at the site grows up over the thrombus so as to enclose it completely from the lumen of the vessel (Fig. 69), and at the same time young capillaries commence to grow from the vasa vasorum and pass through the intima into the thrombus. They are accompanied by young connective tissue cells, and the peripheral part of the thrombus is soon occupied by a zone of vascular connective tissue (Fig. 70). The endothelium covering the thrombus also has vaso-formative properties, and buds grow down from it into the substance of the thrombus. It is generally accepted that, where the lumen is not actually destroyed, as by ligature, these buds may grow through the thrombus and communicate with similar capillary buds coming from the other side ; and that in this way the thrombus may become canalised and a

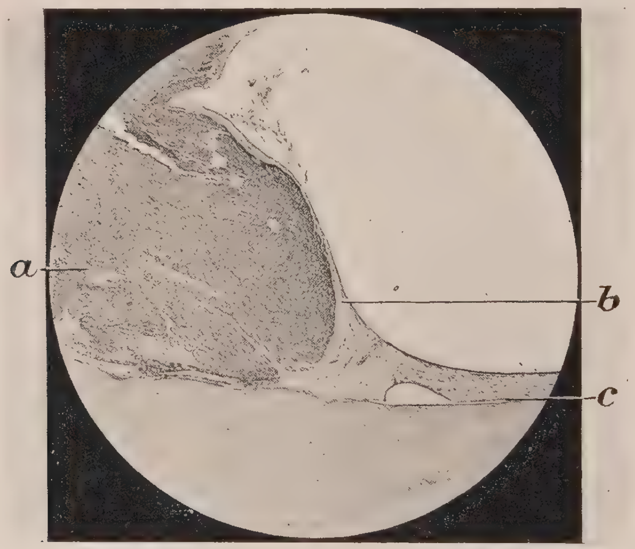

Fig. 69.—Section of Thrombus showing Growth of Endothelium over the surface.

(*a*) Thrombus ; (*b*) growth of endothelium and fibrous tissue over thrombus from (*c*) intima. (D. F. C.) × 35.

new channel for the circulation may be established. In most cases of thrombosis occurring naturally, however, where the channel is restored, this occurs by shrinking of the thrombus from the wall of the vessel. Ultimately, the thrombus may become completely occupied by the young tissue and then there follows formation of fibrous matrix and shrinking of the tissue. The muscle cells disappear and ultimately only a fibrous cord may be left. When the thrombus has been slowly formed and is of dense character, the process of organisation may occupy a considerable time, and if the wall of the vessel is diseased the organisation may be indefinitely delayed and calcification may occur in the thrombus.

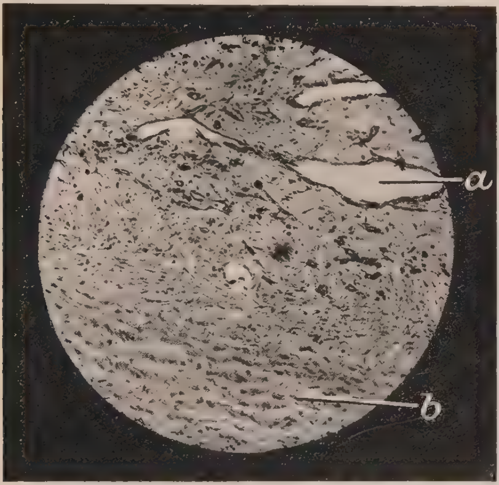

Fig. 70.—Partially organised Thrombus in Vein.
(*a*) Newly formed capillaries invading the thrombus; (*b*) media. × 60.

Organisation of Exudate. When there is inflammation of a serous membrane attended by fibrinous exudation, organisation of the fibrin occurs, and proceeds on similar lines. In such a case the serosal cells have become destroyed and the lymphatic spaces of the membrane are thus in communication with the serous cavity. If the fibrin be in the form of loose reticulum it may be partly absorbed by leucocytes, and the endothelial covering may be repaired to a certain extent; accordingly the dense fibrous adhesions which ultimately form may be only partial. If, however, the fibrin be abundant and especially if it be dense, it becomes absorbed by a process of organisation. A zone of young connective tissue cells and young capillaries is formed in the superficial parts of both the visceral and parietal layers. The two zones then advance from the opposite sides through the masses of fibrin, leading to its absorption, and ultimately coalesce. After this has occurred the process of devascularisation again takes place, and the result is fibrous adhesion of varying extent between the layers.

Repair and Hyperplasia of Various Tissues

We shall now consider the proliferative capacity shown by different cells in the process of repair, and with this it will be convenient to include proliferation in processes of hypertrophy, in response to increased demand for functional activity.

Blood Cells. Repair of the cells of the blood is of course constantly going on, and becomes increased when the cells are being lost. Regeneration of *red corpuscles* after hæmorrhage may become complete in a relatively short time, but if hæmorrhage be oft repeated then the regeneration becomes less active, and a condition of anæmia may persist for some time after the cause has been removed. The increase of red corpuscles is supplied by a more active proliferation of erythroblasts, which are fairly large and contain little hæmoglobin. The erythroblasts arising from them acquire more hæmoglobin and lose their nucleus, which has become smaller and more condensed. The young erythrocytes thus formed enter the circulation, where they are recognisable for some time by their having a slightly basophile reaction and by their containing a reticulum stainable by special methods. The number of such corpuscles, called reticulocytes, supplies an important evidence of the amount of regeneration going on (p. 437). Erythroblasts of the normoblast type may also be present in the circulation with them. What may be considered a process of *compensatory hyperplasia* is seen in the increase in the number of red corpuscles which occurs when a person resides in a high altitude (p. 434). The supply of *leucocytes* seems to be almost unlimited, as is illustrated by the large quantities of pus which may be discharged during a long period. The process, which has already been discussed, is of the nature rather of a compensatory hyperplasia, in response to demand, than of repair after loss, and the stimulus is usually the action of toxins (p. 77).

Connective Tissues and Blood Vessels. New formation of connective tissue and capillaries takes place with rapidity as has been described, and becomes excessive when there is repeated damage to or loss of the new cells. Endothelial cells have great proliferative capacity, and this may be directed either to providing a supply of phagocytes or, in the case of serous sacs, to the repair of the surface which has lost its endothelium. Elastic tissue can be formed anew and in some chronic inflammatory condition may be in great excess, but the mode of formation of the fibres is imperfectly understood. It is usually defective in ordinary healing, and the special arrangements are not restored in the case of the skin. In endarteritis obliterans, however, where young connective tissue is formed in the intima of arteries, new elastic laminæ with regular arrangement are often seen.

Further, increase of elastic tissue, as a hypertrophic process, occurs in arteries when there is increased pressure, and new laminæ may be split off from the internal elastic lamina, or may be added to old laminæ. *Bone* has remarkable powers of repair (p. 807), which follows the same general laws as that of the soft connective tissues—we see the same active proliferation of the osteoblasts to occupy the gap or defect, and then the formation of matrix by them, just as the collagenous fibres are laid down by the connective tissue cells. And when the damage is continued, as in septic lesions of bone, there results excessive formation of dense sclerotic bone, which is just the homologue of scar tissue. *Cartilage* cells have little power of proliferation, in fact some writers state that the adult cells cannot multiply, these being end products. A wound of, or damage to, cartilage is ordinarily repaired either by the formation of new cartilage cells from the deep layer of the perichondrium, or by an ingrowth of young connective cells and capillaries.

Muscle. When ordinary striped muscle is cut across, the sarcolemma cells near the injury undergo proliferation and come to form multi-nucleated plasmodium-like projections which grow outwards Fig. 71). In these differentiation into striped sarcous material may occur, but there is no effective restoration of muscle by this method. The process is slow, and before it has advanced any considerable distance, the connective tissue cells with new blood vessels have filled up the gap; thus actual union of severed muscles takes place by ordinary connective tissue. When a portion

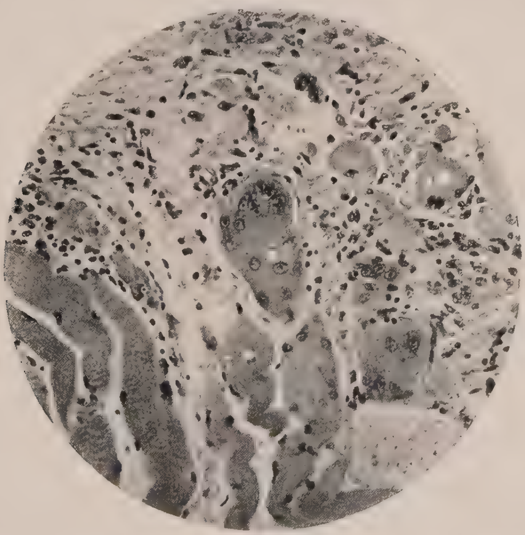

FIG. 71.—Striped Muscle in Granulation Tissue showing multiplication of Sarcolemma Cells and formation of Plasmodium-like Structures. (D. F. C.) × about 175.

of muscle is destroyed by a toxic agency, as sometimes occurs, the sarcolemma cells aided by leucocytes absorb the dead material, and then the defect may be repaired by the laying down of new sarcous substance by the former. Wounds of heart muscle and non-striped muscle are repaired by ordinary connective tissue, though the non-striped muscle cells proliferate to a certain extent by mitotic division. On the other hand, muscle tissue has marked power of *hypertrophic growth.* In the case of striped muscle this occurs merely by the enlargement of the individual fibres; but in the hypertrophy of non-striped muscle there occur both enlargement and proliferation of the muscle cells. In a hypertrophied heart, the individual muscle cells are distinctly enlarged, increased in length and thickness. Some contain two nuclei and there is at times an appearance suggesting longitudinal division of the cell. It is doubtful, however, whether this actually occurs, and certainly the increase in the size of the individual fibres seems sufficient to explain the increase of muscle as a whole.

Epithelia. Epithelial cells generally have marked regenerative power. This is especially seen in the covering epithelia of the skin and mucous membranes, and large defects are satisfactorily healed over. Further, in the new epithelium we may find restoration of the characteristic arrangements. But in the case of organs such as the liver and kidneys, when a wound occurs, repair takes place by connective tissue; for although there is proliferation of the specialised cells, this is relatively slow and cannot keep pace with that of the connective tissue cells. For example, at the margin of a partly healed rupture of the liver, there are to be seen budding processes of epithelial cells with irregular acinus-like arrangement, and the origin of these can be traced to the liver cells as well as to the bile-duct epithelium (Fig. 72). Such growth is the result of breach of continuity, but it is of limited extent and becomes arrested in the condensing connective tissue. It is an example of an ineffective attempt at repair, this occurring by means of connective tissue. If, however, the specialised cells be destroyed, without the supporting tissue being involved, repair may be effected by the adjacent specialised

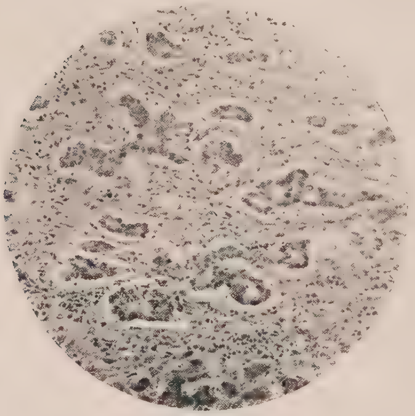

FIG. 72.—Healing Laceration of Liver, showing irregular masses of Epithelial Cells which have grown out from the Liver Cells and Bile-ducts.

A few liver cells are present in lower part of figure. × 150.

cells, the necrosed cells being absorbed. Mitotic figures may be seen in liver cells in the neighbourhood of a necrosed portion of a column; and there is evidence that considerable areas of focal necrosis may be thus healed without leaving any trace. So also in the kidney when cells of the convoluted tubules are killed by toxic agencies and desquamated, repair may be effected by the surviving cells; in this case again without any connective tissue growth.

As a rule the power of *hypertrophy* and *hyperplasia* is a well-marked feature of specialised epithelium, and in this way a large portion of functioning tissue, e.g. liver, may be restored, when a portion of the organ has been destroyed (*vide* p. 121). The growth in such cases represents a response on the part of the surviving cells, at a distance from the injury, to increased functional demands, and is thus not the *direct* result of breach of continuity. The term "regeneration," which means a reproduction or re-formation of what has been lost, should not be applied to such a process, though this is sometimes done.

Nervous Tissue. Nerve cells when once fully formed have no power of proliferation; once lost they are so permanently. The various parts of the cell may, however, be repaired so long as the cell remains alive, and the most striking example of this is the growth in a peripheral direction of the axon, as seen after nerve section or destruction of nerve fibres. Neuroglia cells have great powers of proliferation, and repair is effected by them if the lesion is confined to the nervous tissue proper. If, however, it affects also the ordinary connective tissue which accompanies the blood vessels, growth occurs in this also, so that often both types of connective tissue are involved.

HYPERTROPHY

This term means increase of the essential tissue of an organ, e.g. the muscle cells of the heart, liver cells, etc. Such increase may depend upon enlargement of the individual cells—*hypertrophy* proper, or there may be at the same time proliferation of the cells—*hyperplasia*; the two conditions are often present together. The term, however, is often used in a somewhat loose fashion where there is enlargement of a part. For example, a mucous membrane is sometimes wrongly spoken of as hypertrophied, when it is merely thickened as the result of interstitial increase, leucocytic infiltration, etc. Also retention of secretion, e.g. in the thyroid gland, may produce an enlargement which is not a true hypertrophy. The key to hypertrophy occurring in abnormal conditions is given by physiological hypertrophy, the most striking example of which is seen in the case of hypertrophy of the uterus and mammary glands, which occurs during pregnancy. Such an enlargement represents an adaptation to increased functional demands, and a similar principle dominates in pathological hypertrophy. Hypertrophy is, of course, the opposite condition to atrophy, and the latter may be brought about by a variety of causes (p. 137). The converse of each cause which produces atrophy, however, does not lead to hypertrophy. In the great majority of cases true hypertrophy is brought about by increased functional activity, and it would be better to restrict the term to conditions where it is produced in this way.

Compensatory Hypertrophy. Hypertrophy, in response to abnormal functional demands, is sometimes spoken of as compensatory hypertrophy. It is seen mainly in the case of the *muscular* and *glandular* tissues. The muscular tissue of the heart is capable of great hypertrophy when increased work is thrown upon it, e.g. by valvular disease or by obstruction in the arterial system. The muscular walls become greatly thickened, and the weight of the heart may be twice the normal, or even more. In this cardiac hypertrophy, the muscle fibres are increased in thickness and length, and the enlargement of the individual fibres would appear to be sufficient to cause the increase in muscle (Fig. 73). There is some evidence that division of the muscle cells takes place, i.e. hyperplasia, but if this occurs it plays only a subsidiary part. Hypertrophy of non-striped muscle is of frequent occurrence, and here both enlargement of the individual fibres and hyperplasia occur, though as a rule mainly the latter. Thus there is hypertrophy of the muscle in arteries in response to long-continued high blood pressure (p. 286), and when an artery becomes permanently enlarged for purposes of collateral circulation, there is hypertrophy of the various elements in its wall. The wall of the urinary bladder may become greatly hypertrophied when there is obstruction to outflow of urine, e.g. in cases of enlarged prostate, stricture, etc. So also when there is stenosis of the bowel, for example

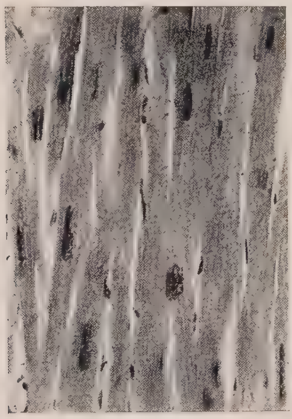

FIG. 73.—Hypertrophied Muscle Fibres of Heart in a case of Arterio-sclerosis with high Blood Pressure. × 200.

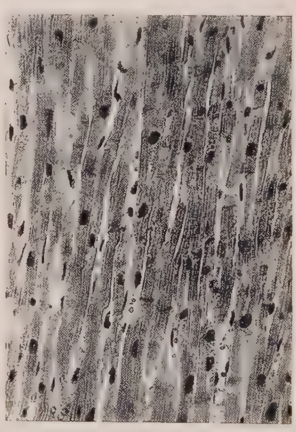

FIG. 74.—Slightly Atrophied Heart Muscle; to compare with Fig. 73. × 200.

as the result of tumour, the wall of the part above often undergoes hypertrophy.

With regard to glandular organs, it may be stated as a general rule, that when a part of the organ is destroyed, the surviving part endeavours to compensate by hypertrophy and hyperplasia. Thus, when a large part of the liver is removed experimentally, hypertrophic changes occur in the surviving portion, and ultimately the original weight may be restored. In such a case the liver cells become enlarged and then undergo division, so that each individual lobule is increased in size. There is, however, no formation of new lobules, that is, no regeneration in the strict sense. Similar hypertrophic processes are seen in the human subject when liver tissue is destroyed by disease. It may be a marked feature in cirrhosis of the liver (Fig. 75), in chronic venous congestion and in cases where part of the liver is destroyed by tumour or by hydatid cyst. Similarly, in the kidneys hypertrophy may occur in the surviving tubules, when others have been destroyed as the result of chronic inflammation or arterial disease, although in this case it may be prevented by the abnormal state of the kidney tissue. In the case of paired organs the hypertrophy of one following on defect of the other is often spoken of as *vicarious hypertrophy.* When one kidney is removed, or destroyed by disease, the other may undergo hypertrophy, and this occurs to a greater degree when the loss has taken place in the earlier years of life. For example, congenital absence of one kidney often leads to the other organ being double the size of the normal. In a similar way, loss of one adrenal or one testis may be followed by hypertrophy of the surviving organ. When one lung becomes collapsed, the other becomes increased in size; in this case the mechanical factor of overstretching plays the chief part. But it has been found that when the lesion is in early life, a formation of new alveoli takes place in the surviving lung. Lastly, it may be mentioned that hypertrophic growth of bone occurs in response to strain, etc., for example, the hypertrophy of one bone of the forearm when the other has been removed or rendered useless.

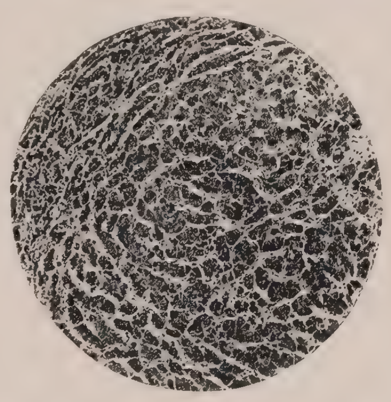

Fig. 75.—Islet of Hypertrophied Liver Cells from a case of early Cirrhosis.

Note the stretching of the cells at the periphery. × 60.

In all these cases we see a principle analogous to what is seen in the case of atrophy (p. 137). Just as maintenance of size demands sufficient katabolism, so also excessive katabolism brings about excessive anabolism or building up of the molecules lost, and thus leads to enlargement of the cell. In other words, within certain limits, there is a relation between the size of the cell and the functional requirements. Beyond a certain stage the requirements can no longer be met by mere enlargement of cells and then hyperplastic proliferation occurs.

It will be seen that in the examples given of compensatory change hypertrophy and hyperplasia, as defined above, are present together in varying degree. In certain instances, however, notably in connection with the hæmopoietic tissues, the change is purely a proliferative one without enlargement of the cells, that is a pure compensatory hyperplasia. For example the demand for increased supply of erythrocytes or leucocytes is met in this way.

Relation to Blood Supply. Other factors are often considered to play a part in the production of overgrowth of tissue. It has been supposed by some that such a result may be due to increased supply of nourishment, especially to an increased arterial supply. An experiment performed by John Hunter is often quoted in support of this. He transplanted the spur of a cock from the leg to the vascular comb, and found that it grew to an abnormal size. This has been supposed to be due to the great vascularity of the new site, but it should be borne in mind that, in the new situation the spur was not exposed to the usual attrition which occurs in its usual situation. The experiment cannot, therefore, be accepted as an unequivocal example of hypertrophy due to increased blood supply. The division of the sympathetic in the neck may lead to some thickening of the skin, but there is no true hypertrophy of the parts as a result of the vascular dilatation. We may sum up by saying that, although interference with the blood supply produces atrophy, there is no satisfactory evidence that either excessive assimilation of food or increased blood supply can produce true hypertrophy, that is, enlargement and proliferation of cells.

Relation to Intermittent Pressure. Another cause of hypertrophy frequently mentioned is intermittent pressure, there being here the contrast to the atrophy which results from constant pressure. The example usually quoted is thickening of the epidermis, which results from hard manual labour, that is, intermittent pressure; but in this case what chiefly happens is damage to, and loss of, the superficial cells, in consequence of which repair occurs; and when damage is repeated, the repair becomes an over-repair. There is also increase of horny material, which is an indication of increased functional activity. A similar principle applies to other cases of this kind.

Relation to Endocrine Glands. It has already been stated that certain of these glands have an important relation to the growth and nourishment of the tissues; for example, deficiency of the thyroid may bring about either hypoplasia or atrophy (p. 930). The most striking example of the converse is seen in the case of the pituitary, where hyperactivity brings about giantism or acromegaly (a condition in which there is enlargement both of bone and soft tissues), according as the lesion occurs in early or adult life. Further, there is an inter-relation between the different endocrine glands as regards both functional activity and size ; deficiency of one may lead to enlargement of another, and this may be of the nature of a compensatory hypertrophy, though more probably it has another significance. In the hyperactivity of the thyroid met with in exophthalmic goitre there is often an accompanying hyperplasia of the thymus, but the interpretation of this change is not clear. It is also known that the normal hyperplastic changes in the mammæ in pregnancy are brought about by the action of hormones either from the corpus luteum or from the fœtal tissues. There is thus ample evidence that overgrowth of functioning tissues may be produced by internal secretions, and known examples of this are steadily increasing, as will be illustrated in subsequent chapters.

Relations to the Nervous System. There are various examples of enlargement of tissues due to lesions of the nervous system, such as overgrowth of the skin epithelium, of nails, and occasionally of bone. These need not be analysed in detail, but they may be said in general to be the result of trophic disturbance. A similar statement applies to the increased size of the muscles in pseudo-hypertrophic paralysis, where, as already explained, the enlargement is due simply to a great accumulation of fat or lipomatosis, which occurs amongst the atrophied muscle fibres.

In certain conditions enlargement of important tissues occurs without known cause. This is the case in the pathological hypertrophy of the mammæ (p. 904), which sometimes reaches an extraordinary degree, and also in the so-called hypertrophy of the prostate, which is of so common occurrence.

In all cases it is important to distinguish the two main types of true hypertrophy, namely, (*a*) that occurring in response to increased functional activity—*functional hypertrophy*, and (*b*) that brought about by the influence of hormones—*hormonic hypertrophy*.

METAPLASIA

By this term is meant the transformation of one tissue into another. In other words, we may say that metaplasia occurs when a differentiated tissue loses its characters and assumes those of another differentiated tissue. In the process of ontogenetic development, there is a process of differentiation, whereby the various functional properties and powers are distributed out to the different tissues and organs, in relation to their anatomical arrangements. Ultimately each tissue has its peculiar structure and function, and in the human subject the differentiation is almost complete. Nevertheless, a certain amount of interchange between the tissues is possible, but only between those of the same group. A connective tissue cannot become changed into an epithelial tissue, or *vice versa* ; and in the case of epithelia, metaplasia occurs only amongst those which have a covering or protective formation, i.e. those of the skin, mucous membranes and ducts of glands —not between epithelial cells with specialised functions.

Metaplasia may be said to be the result of alteration in the conditions of life of the cells, and usually represents an adaptation to changes in environment and functional demands. In the case of the epithelial tissues the change is often the result of chronic irritation, and a more resistant type of epithelium is produced. Thus, stratified squamous epithelium may form in the gall-bladder, in the pelvis of the kidney, in the bronchi, in the mucous membrane of the nose or the ducts of the salivary glands. In extroversion of the urinary bladder, the transitional epithelium may become changed into mucin-forming columnar epithelium, or even into stratified squamous epithelium. Amongst the connective tissues, metaplasia occurs between ordinary fibrous tissue, myxomatous tissue, bone, and cartilage. Bone formation may be met with occasionally in the walls of diseased arteries, in the coats of the eye, in the region of calcareous deposits, etc. In the healing of fractures, metaplasia into cartilage may occur, especially where there is undue mobility (p. 808).

A remarkable example of metaplasia is that met with in vitamin A deficiency. In this condition, in addition to xerophthalmia, there occurs a change of cubical and columnar epithelia into stratified squamous epithelium with keratinisation and desquamation of cells. The change is widespread, affecting not merely covering epithelia such as those of nose, bronchi, urinary tract, etc., but also some secretory epithelia, e.g. those of the lachrymal and salivary glands. The change is accompanied by a marked proneness to bacterial infection (p. 180). When the vitamin deficiency is made good retrogression of the metaplasia to the normal type may occur.

The capacity of serosal endothelium to undergo metaplasia has been recently demonstrated in a striking way by J. S. Young. On injecting sudan III in olive oil along with sodium cholate into the pleural cavity of the rabbit, he has found that the flattened serosal cells become at first swollen and globular, and may then assume the characters of a columnar epithelium (Figs. 76, 77). Thereafter the cells proliferate and form several layers, which come to resemble a transitional epithelium or even a squamous epithelium in which prickle cells are present. Metaplasia also occurs in the alveolar epithelium nearest to the pleura, the cells becoming cubical or columnar in form. Corresponding changes followed injections of strontium chloride, which Loeb found very effective in producing parthenogenesis in the eggs of the sea-urchin, but in this case retrogression of the metaplasia occurred pretty rapidly. These results are of importance not only in showing the metaplastic properties of the serosal cells, but also in demonstrating the remarkable effect of substances which act as special stimulants of cellular activity.

Metaplasia is to be distinguished from a mere loss of the special characters of cells, which may ensue when their function is interfered with. In this condition, which may be called *retrogression* of a tissue, the cells may be said to become de-differentiated. Cells of glandular organs often become smaller, more cubical, and lose their special features. Thus liver cells may come to resemble those of bile-ducts, and in a fibrotic and collapsed lung, the alveolar epithelium may assume a cubical form. In *tumours* true metaplasia is often met with, but sometimes it is simulated as a result of cells undergoing differentiation in their growth. Thus in a tumour of the kidney, not uncommon in children, we may find, in addition to a cellular tissue, imperfectly formed tubules and even glomeruli. The appearance of transition between the tissues in this case is simply due to the fact that the tumour has taken origin from the cells destined to form kidney tissue, before they have undergone differentiation. Again, the appearance of metaplasia may be produced owing to abnormalities in the process of development. For example, stratified squamous epithelium may in this way occur in the mammary gland or in the thyroid. Lastly, the characters of the tissue may become changed, not by transformation, but by one tissue replacing the other. Thus, the fatty marrow of the long bones is, in certain conditions, replaced by red hæmopoietic marrow. In this instance, the growth of the latter takes place from small centres between the fat cells (p. 516), but there is no transformation of one tissue into the other in the strict sense. These examples show that care must be taken in using the term metaplasia, and in every case the condition causing the apparent transition must be enquired into.

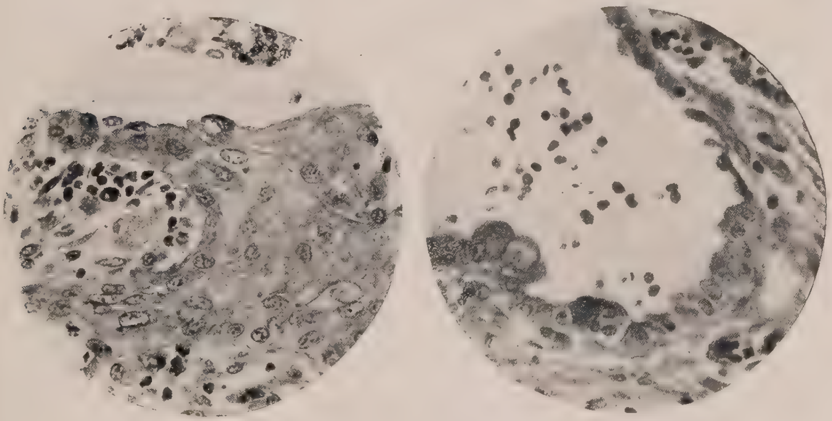

Fig. 76. Fig. 77.

Figs. 76, 77.—Metaplasia of Serosal Cells of Pleura of Rabbit produced by Injection of Sudan III and Sodium Cholate.

In Fig. 76 the cells have become spherical and are stratified, whilst in Fig. 77 they are more of columnar shape. (J. S. Y.) × 300.

CHAPTER IV

DISTURBANCES OF NUTRITION

NECROSIS, DEGENERATIONS, INFILTRATIONS, ETC.[1]

Introductory. In this chapter we shall consider the various structural changes which represent the results of *damage* to cells, or interference with their normal life and metabolism. This statement must, however, be taken as a general expression, as some of the changes may possibly represent reactive processes or increased function of the cells. The changes to be considered are sometimes classified as *retrogressive*, in contrast to the *progressive* changes which represent increased cellular activity and proliferation. We may say that the chief causes of these retrogressive changes are interference with the proper supply of nutriment, on the one hand, and the action of poisons, on the other. The extreme degree of damage is death of cells, or *necrosis*, and when this is accompanied by putrefaction the term *gangrene* is applied. Impaired supply of nutriment or other causes may lead merely to diminution in the size of cells or tissues, and this is spoken of as *atrophy*. Then there is the important group of what are called degenerations. The term *degeneration* is difficult to define accurately, but it may be said to include the visible alterations in living cells, apart from simple atrophy, which are produced by disordered nutrition and represent damage short of actual death. Again, metabolic disturbances are often accompanied by the appearance in the cells of definite substances—fat, glycogen, pigments and the like—and these are either normal constituents in excess or abnormal substances. The term *infiltration* is then applied to such accumulations—fatty, glycogenic, etc. The use of the terms degeneration and infiltration is convenient, but it is sometimes not possible to draw a distinction between them, and degeneration is often accompanied by infiltration. Nevertheless, there are examples of infiltration of definite substances occurring without any evidence of damage to the cell; on the contrary, the infiltration sometimes represents a process of economic value to the body. An example of this is the storing of iron in the form of granular pigment within the cells, when there has been excessive destruction of blood. The substances seen in infiltrations are, for the most part, normal constituents of the fluids and tissues or derivatives from such constituents, but they may also be of exogenous origin, that is, derived from outside. The subjects to be dealt with thus include necrotic and atrophic changes, degenerations and infiltrations, but it must be understood that more than one type may be present in the conditions described below under separate headings.

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[1] For a full account of the chemistry of this and other subjects the student is referred to *Chemical Pathology*, by Gideon Wells, 5th edition, Philadelphia and London, 1925.

NECROSIS

By necrosis is meant death of a cell or groups of cells, when they still form part of the living body. Death of cells may occur suddenly, for example as the result of heat or chemical agents, etc., or it may occur gradually and be preceded by structural signs of degeneration and disintegration; in the latter case, the term *necrobiosis* is often applied. Cells in process of dying are known to undergo physical changes, for example in conductivity and permeability. Living cells when placed in a weak solution of neutral red, are not penetrated by the stain and their nuclei are not stained. When the cells die, however, the cytoplasm becomes permeable and the nuclei become coloured by the dye. But it is generally agreed that the process of dying is a gradual one and that it is not possible to state the actual point at which the vital functions are irrevocably lost. The exact changes underlying cellular death often cannot be defined and we can only say that death means permanent cessation of the functions of the cells. The actual death in this sense of a previously healthy cell may not be attended by any visible sign, but there soon follow histological changes which enable us to infer that the cell has been dead for some time before the tissue has been fixed. These signs of necrosis, which are of great importance in the histological examination of the tissues, are accordingly of secondary nature; they are of post-mortem occurrence so far as the cell is concerned. To put the matter in another way, when a piece of living tissue is placed in a fixing fluid, the cells are, of course, killed, but the structural details are preserved. On the other hand, when the tissue remains a constituent of the living body for some time after being killed, important changes follow, even in the absence of micro-organisms. The only exception to the latter statement is that when the tissue still forming part of the body is killed by a chemical coagulant which also fixes the tissue, the changes indicative of necrosis do not occur.

Causes of Necrosis. These may be grouped under the following three heads:—

(*a*) *Deprivation of Blood Supply.* This is frequently seen when an artery is obstructed from any cause in a situation where the collateral anastomosis is insufficient to keep the part alive, the common result being an *infarct* (p. 25). It is seen also in connection with bone when a suppurative lesion, occurring within and outside it, destroys all the vascular connections (p. 811). It may be noted that the deprivation of blood which produces necrosis may not necessarily be of permanent character. Any tissue is able to survive complete cutting off of the blood supply for only a definite period, and this period varies in the case of different tissues, some having greater powers of survival than others. This has been discussed more fully above (p. 28).

(*b*) *Action of Toxins*, especially those of bacterial origin. Many bacteria produce substances which act as cell poisons and produce necrosis. This is a prominent feature in the case of the tubercle bacillus, the result being a central necrosis of the tubercle nodule ; it is well illustrated also in the action of the diphtheria bacillus on the mucous membrane of the pharynx, here also necrosis being produced. In the production of necrosis, common in inflammations, both toxic action and interference with the circulation are often concerned. Moreover, such toxins act not only locally around the bacteria, but also on distant parts, notably on the kidneys, liver, heart, etc., and the cells of these organs may in this way undergo necrosis. A degree of toxic action insufficient to cause necrosis leads to various degenerative changes, from which the cells may recover.

(*c*) *Chemical and Physical Agencies*—caustics, extremes of heat and cold, electricity, etc. The action of many chemical agents of a simple nature can be explained by their effects on proteins outside the body. For example, some, such as carbolic acid and corrosive sublimate, act as coagulants of the cell protoplasm, alkalies lead to softening and liquefaction, whilst sulphuric acid produces hæmorrhage and blackening, so that a dark eschar results. Such effects are well illustrated by the lesions in the stomach in cases of poisoning with such agents (p. 532). As a rule, these chemical substances, in a dilution insufficient to cause death, produce inflammatory changes ; this is often seen at the margin of the parts actually necrotic. Cells are very sensitive to the action of heat, and it may be said that exposure to a temperature of 45° C. causes cell death, though the duration necessary varies in the case of different cells. Cold, on the other hand, has little direct action. Certain tissues can be frozen without being killed, and it has been shown that cancer cells kept in a frozen state for a considerable time are still capable of multiplying and producing a growth. The occurrence of necrosis after frostbite is due to damage of the capillaries, so that extreme stasis and formation of hyaline thrombi result in them ; and the restoration of the circulation when the part is warmed is rendered impossible. Thrombosis extends also to the arteries, and obliterative changes may be found at a later period.

The presence of lesions of the *nervous system* favours the occurrence of necrosis, but there is no evidence that such lesions can, in themselves, bring about the death of tissues.

Structural Changes. The changes following necrosis of a portion of the tissue are of two main types.

(*a*) The more common result is that the tissue becomes somewhat firmer and usually somewhat swollen, dull and lustreless, and of a yellowish tinge, unless it contains much blood. To this type Weigert applied the term *coagulative necrosis*, his view being that the dying cell absorbs lymph, and that then an intra-cellular coagulation takes place by enzymes which are set free within the cells at the time of their death. The process, in fact, closely corresponds with the coagulation of fibrinogen when it is brought into contact with damaged tissues, and the enzymes are probably of the nature of thrombokinase. It has been disputed whether this is exactly what occurs, but it can hardly be doubted that the process is allied to coagulation, and the term is a convenient one.

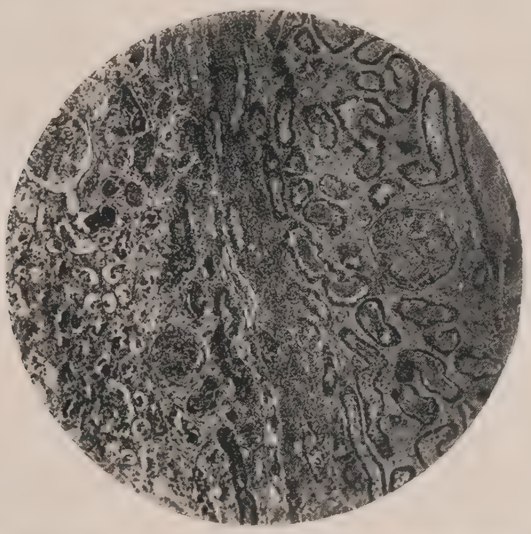


Fig. 78.—Infarction in kidney ; the right half shows the appearances of necrosed tissue, the left half is unaffected. × 60.

(*b*) In the other type, the affected tissue loses its consistence, becomes softened and ultimately liquefied. To this process of softening, Weigert applied the term *colliquative necrosis*. It is seen in tissues rich in fluid, and notably in the central nervous system ; it is really an instance of autolysis or self-digestion (p. 132). For example, when a nutrient artery is blocked, the brain substance loses its consistence, becomes pulpy and is ultimately changed into a turbid fluid.

On microscopic examination of a tissue which has undergone *coagulative* necrosis, it is found that the cell protoplasm has lost its characteristic structural appearance, has become partly granular and partly homogeneous and more or less structureless, while its outline may be irregular or broken. Nevertheless, the structural outlines of the tissue are maintained in the dead tissue for a long time (Figs. 78–80); in an infarct of the kidney, for example, the necrosed tubules and glomeruli are recognisable for weeks after the occurrence of necrosis. The nuclei of the dead cells also undergo important changes, of which there are two main types. In the one type, the nucleus gradually loses its staining reaction, until ultimately the whole cell stains uniformly, though the outline of the nucleus may still be recognisable for some time. This change, as it is apparently due to solution of the chromatin, is called *karyolysis.* In the other type, the chromatin breaks up into darkly staining small masses or granules, which are sometimes prominent just inside the nuclear membrane; later they are irregularly arranged in the cell protoplasm. This process is known as *karyorrhexis* (Fig. 81). Sometimes the chromatin becomes collected into a few dense and deeply staining fragments, the appearance being then called *pyknosis.* These nuclear changes also depend on the action of an intracellular enzyme set free on the death of the cell, the nucleo-protein being gradually split up into simpler compounds and nucleic acid

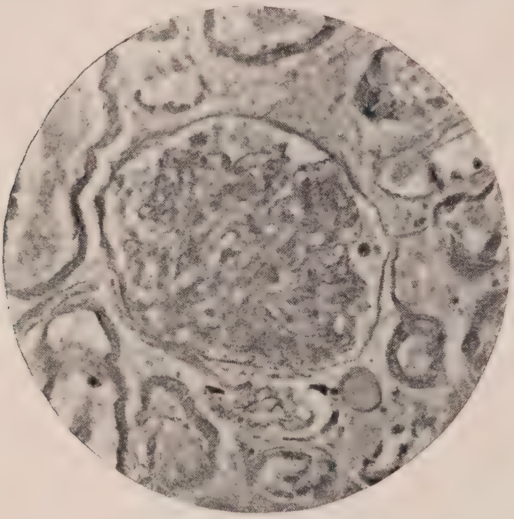


Fig. 79.—Portion of Infarction of Kidney, showing Necrotic Change.

A glomerulus and tubules are seen, but the nuclei have disappeared and the structural details are lost. × 250.

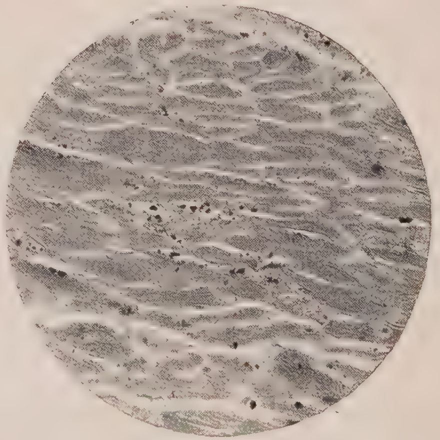


Fig. 80.—Coagulative Necrosis in Infarction of Heart Muscle.

The dead fibres are hyaline and structureless; remains of leucocytes are present between them. × 250.

being ultimately set free. The appearance which results would seem to depend, in part at least, on the amount of chromatin present in the nucleus. If this is relatively scanty, as in the kidney and liver cells, the basophile constituents, to which the nuclear staining is due, diffuse out, and the appearance of karyolysis results. If, on the other hand, the chromatin is abundant, as in the nuclei of leucocytes, karyorrhexis is the common occurrence. This, however, is not the whole explanation as variations in the nuclear changes are met with in the same type of cell. Granules formed from the nuclear disintegration, probably containing a large proportion of nucleic acid, have considerable powers of persistence, and can often be seen as deeply stained particles in old necrotic areas.

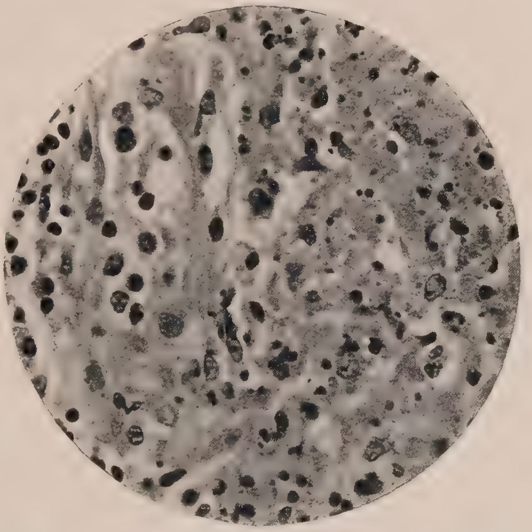


FIG. 81.—Spreading Necrosis with Karyorrhexis in Lymph Gland in Typhoid Fever.

Note destruction of nuclei and numerous deeply-stained granules of chromatin. The tissue to left of field is still healthy. × 500.

In *colliquative* softening, the tissue elements absorb water and then disintegrate. This is well seen in the central nervous system, where the myelin and axis cylinders become irregularly swollen and soon break down, fats and lipoids being set free. Neuroglia also becomes softened and ultimately dissolved. In other words, lytic processes predominate, and this is apt to be the case when a tissue contains much fluid. In connection with the occurrence of necrosis due to the stopping of arterial blood supply, it is important to note that different cells show great variation as regards both the period and the degree of deprivation necessary to kill them, the more specialised cells suffering first. It has been found that, if the blood supply to the kidney be temporarily stopped and then restored, the cells ultimately die if the blood has been cut off for two hours and, in the case of the central nervous system, a much shorter time of deprivation, probably a few minutes, will be effective. Again, at the margin of an infarct of the kidney the epithelial cells will be found to be dead, while the connective tissue cells have survived—another evidence of varying susceptibility. The ordinary surgical use of the tourniquet in operation on the limbs shows that deprivation of blood supply can be tolerated for a considerable time. Death of tissue, however, may follow if this is exceeded; for example, subsequent necrosis of muscle has been observed when a tourniquet has by mistake been left in position too long.

Autolysis. The various changes following death of cells have now been shown to be due to enzymes contained within the cells. During the life of the cells these enzymes, which are no doubt concerned in the normal metabolism, have a balanced or harmonious working, and this may be disturbed by various causes, the deprivation of oxygen being one of the most important; certain of the enzymes then act in excess and bring about the changes described. The term *autolysis* has been applied to the digestive softening of tissues produced by their own enzymes. Such enzymes may be derived from the dead cells themselves—autolysis in the strict sense—or may be produced by other cells, especially leucocytes—*heterolysis.* The latter may be seen often in comparatively firm tissues, provided numerous leucocytes are present, and is the main feature in suppuration. The leucocytes produce the softening by means of proteolytic enzymes which they form (p. 80). Autolytic processes come into play after the death of the individual, and bring about changes in the cells and their nuclei, of nature corresponding to those seen in necrosis. A pneumonic lung may thus become softened and almost puriform in places, and the softening of the spleen, which is often a notable feature in septicæmia, is, to a large extent, an autolytic phenomenon, occurring *post mortem.* The changes seen in cloudy swelling (p. 141) are accentuated in the same way; the damaged cells lose the nuclear staining much more readily than do normal cells.

The nature and effects of autolysis can be studied outside the body by incubating tissues in aseptic conditions, or under a suitable antiseptic, such as toluol, which does not injure the enzymes. If portions of kidney or liver be incubated for varying periods of time, then fixed and examined microscopically, autolytic changes, closely corresponding to those in necrotic tissues, are seen to occur. If, on the other hand, the tissue has been exposed to a temperature of 55° C. for an hour, before being placed in the incubator, the tissue remains almost unchanged, and the nuclear staining is retained for almost an indefinite time. This, of course, shows that the autolytic enzymes are destroyed at the temperature mentioned. Again, if the fresh tissue be placed aseptically into isotonic saline and incubated, it will be enormously swollen at the end of twenty-four hours. The explanation of this is that the autolysis leads to breaking down of the larger molecules and consequent increase in the number of molecules; the osmotic pressure is thus increased and fluid passes into the tissue. If, on the contrary, the tissue has undergone a preliminary heating to destroy the enzymes, its volume remains practically unchanged when incubated in saline (Cruickshank). These results explain why dead cells in a fluid as a rule become swollen, but the osmotic phenomena will occur only so long as the cytoplasm is bounded by something corresponding to a membrane. Furthermore, autolysis has been studied by chemical methods and is found to vary in activity in the case of different organs, the liver being especially suitable for the study of the process, owing to its richness in enzymes. Autolysis leads not only to the formation of proteoses, but also to the splitting up of these into amino-acids. Hæmoglobin is broken down by the enzymes of the liver cells, till ultimately the stage is reached when the iron gives a Prussian blue reaction. The presence of glycolytic and lipolytic enzymes has been similarly demonstrated.

Results of Necrosis. The presence of a portion of dead tissue brings about a reactive process which leads to gradual absorption, if this is incomplete, to encapsulation by fibrous tissue. Leucocytes, which are active producers of proteolytic ferments, are the agents chiefly concerned in absorption. In acute yellow atrophy of the liver, however, the autolytic enzymes of the dead liver cells lead to their digestion and absorption, and in this way the cells may entirely disappear from certain areas. If a dead part is of considerable size, e.g. an infarct, complete absorption cannot be brought about, and it becomes encapsulated by fibrous tissue and then gradually shrinks ; but the necrotic remains may persist for a long period, sometimes becoming calcified. So also an area of necrotic softening in the brain becomes surrounded by a zone of proliferated neuroglia, and, as the softened material ultimately becomes liquefied, a cyst-like space results (p. 730).

Caseation. The term signifies the process of becoming cheese-like in appearance, and this commonly follows in necrotic areas of fairly firm consistence. It is a very common occurrence in tuberculosis, and is met with also in infarcts, gummata, in inspissated collections of pus, etc. Caseous material, like cheese in fact, consists of amorphous protein along with a varying amount of fat in a very fine state of division. Under the microscope, it is structureless in appearance (Fig. 54), finely granular or somewhat hyaline, and in it there may be distinguished minute globules of fat and also granules of chromatin, chiefly derived from leucocytes which have wandered into the part. In tuberculosis, the change occurs more rapidly than in other conditions, and this is due to the special action of the tubercle bacillus, which causes a fusion of the cells as they undergo necrosis ; whereas in necrosis produced by other causes, the cells undergo disintegration less rapidly, and their structural outlines may be recognisable for a considerable period. Caseous material has a marked affinity for lime salts ; it thus frequently becomes calcified and surrounded by a fibrous capsule (p. 171). The caseous material of tuberculous lesions sometimes becomes softened by action of polymorpho-nuclear leucocytes and imbibition of fluid, and may be changed into a pultaceous mass or even into a grumous fluid. The extreme example of the results of secondary leucocytic action is seen in the case of the so-called ‘cold abscesses,’ occurring especially in connection with tuberculosis of the vertebral column.

Fat Necrosis. This is a condition produced in the adipose tissue, mainly of the abdominal cavity, by the action of lipase which has been set free from the pancreas. Small patches of fat necrosis are occasionally met with around the pancreas, in cases of death from various causes. The change, however, occurs on a large scale in lesions of the pancreas, especially acute pancreatitis, and also after injury to the gland. In the affected areas the enzymes split the fat into glycerol and fatty acids ; the former becomes absorbed, whilst the latter are deposited in the cell substance in the form of acicular crystals. The affected cells, at the same time, undergo necrosis, in the production of which trypsin is probably concerned ; and thus there are produced in the fat scattered patches, which have an opaque appearance and dull yellowish colour. They are sharply defined and somewhat firmer than the normal tissue. Such patches may occur in large numbers in the fat of the mesentery, omentum and retro-peritoneal tissue, and have been met with even outside the abdominal cavity. On microscopic examination, the necrosed fat cells have an opaque appearance owing to collections of crystals of fatty acids in their interior, and a zone of leucocytic infiltration may be present at their margin (Fig. 82). At a later period, owing to the affinity of the fatty acids for calcium, the patches may undergo calcification and a fibrous capsule is formed around. Fat necrosis has been produced experimentally by injecting pancreatic juice into the peritoneal cavity of an animal ; and it is not due, as was formerly held by some, to bacterial action. In cases of marked fat necrosis, excretion of lipase in the urine has been found to be associated with the condition.

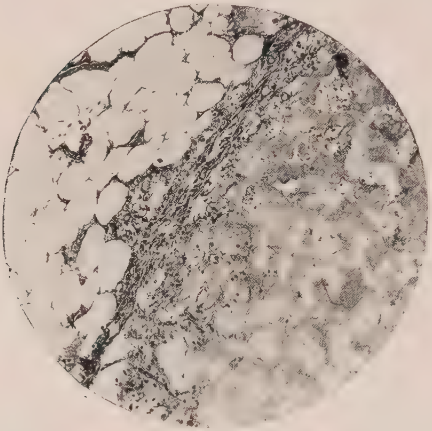


FIG. 82.—Area of Fat Necrosis in Omentum

The dead tissue is to the right and leucocytic infiltration is present at the margin. × 60.

Another form of fat necrosis is that produced by injury to adipose tissue—traumatic fat necrosis. The necrosis is followed by reactive processes leading to a considerable amount of fibrosis around. It occurs especially in the mamma and is considered later in connection with that organ.

GANGRENE

The term gangrene is applied when a dead part becomes the seat of putrefaction ; and the changes then occurring in the dead tissue correspond with those met with in putrefaction outside the body. Various bacteria are concerned in the different stages of the breaking down of proteins, etc., and the ultimate products are substances of comparatively simple nature. Volatile bodies and gases are formed, and to these the foul odour is due. The gases, when they accumulate in the tissues, may give rise to emphysematous crackling. The various changes in colour—to dark brown or greenish brown, and sometimes almost black—are chiefly due to changes in hæmoglobin, and are most pronounced when the part has contained a considerable amount of blood.

Varieties and Structural Changes. Gangrene is sometimes described as being either *primary* or *secondary* in nature. In the former variety the part is supposed to be killed by the putrefying bacteria, whereas in the latter, death is produced by some other cause, e.g. cutting off of the blood supply, and then putrefaction follows. The distinction is not of much importance, and, in fact, the organisms which kill the part are, as a rule, different from those which cause the putrefaction. This is the case, for instance, in the condition known as gas gangrene, an affection comparatively common during the late war. Here, there occurs first of all a rapidly spreading œdema with necrosis of the tissues, usually produced by the *B. welchii.* This organism has practically no power of breaking down proteins, its action being essentially saccharolytic, but the tissues, after having been damaged by its action, become invaded by putrefactive organisms, and thus true gangrene results. The disease called noma is an illustration of the same principle. It is a gangrenous condition which occasionally occurs in poorly nourished children, especially after measles or scarlet fever, or other infection, the site usually being the cheek, where an inflammatory patch of dusky red appearance forms and then becomes darker in colour and ultimately gangrenous. The original necrosis is caused by a characteristic fusiform bacillus, the tissues then becoming the seat of putrefaction. Inflammation of the fauces produced by the diphtheria bacillus may, in a similar manner, become the seat of gangrenous change. The occurrence of gangrene is, of course, favoured by any condition of depressed vitality, and of this a noteworthy example is diabetes, in which an inflammation such as pneumonia is very apt to be followed by gangrene. Occasionally the entrance of putrid fluids into the tissues may be sufficient to cause both necrosis and putrefaction. For example, a cancer of the œsophagus may ulcerate into a bronchus and cause gangrene of the lung; but in most instances of so-called primary gangrene, as has been stated, the death of the tissue is produced by a definite organism and putrefaction caused by other organisms supervenes.

In *secondary gangrene*, death of the tissue is produced by deprivation of the blood supply or by chemical action, and putrefying bacteria then invade the dead part. This result will occur wherever the necrosis involves the skin surface or a mucous membrane to which there is access of the necessary organisms. Thus gangrene of a lower limb is not uncommon in old people as the result of arterial blocking, the collateral circulation being insufficient to keep the part alive. This is known as senile gangrene, and two varieties are distinguished, namely *dry* and *moist.* In the dry type, which is seen in those of spare build, whose tissues contain comparatively little fluid, the skin becomes cold and tallowy in appearance, while the hæmoglobin diffuses out along the veins and produces reddish-purple staining of the tissues. The colour then becomes brownish red and ultimately almost black, whilst the part becomes drier and shrinks, and hence a condition of mummification results. At the junction of the living and dead tissues a line of demarcation becomes established, and a process of slow ulceration ultimately penetrates the soft tissues down to the bone. The moist type of gangrene is seen in a limb where there is abundant fat; it is specially favoured by the presence of œdema. In this form the putrefactive changes occur more rapidly, and blebs of fluid form in the skin. There is sometimes emphysema, owing to the formation of gas by the putrefying organisms, and there is no formation of a line of demarcation; on the contrary, gangrene may spread beyond the part primarily affected.

Moist gangrene is the form met with in *internal organs*. It is a common result when a portion of the bowel has had its blood supply cut off by strangulation, e.g. in a hernial sac. The first occurrence here is interference with the venous return, and the swelling which results leads ultimately to stoppage of the circulation; the part becomes hæmorrhagic and then gangrenous softening takes place. Gangrene of the moist type is met with also in the appendix, pancreas, lungs, etc.

As regards the *conditions of occurrence* of gangrene of a limb or part of a limb, the following summary may be given. The gangrene most frequently met with is of the senile type and is caused by arterial thrombosis resulting from advanced atheroma or calcification of the media (p. 298). In diabetes gangrene is not uncommon as the result of atheroma, which tends to be marked in this disease. It is further to be noted that gangrene may occasionally be met with in middle adult life, and then it is usually due to thrombo-angeitis (p. 306), a disease which affects multiple arterial branches, especially in the lower limbs. Another occasional cause is the spasmodic contraction of arteries which is met with in Raynaud's disease (p. 310). Finally, we may mention that gangrene, usually of a finger, occasionally results from carbolic acid applied as a dressing; the solution is sometimes allowed to dry and then the concentrated acid kills the tissues.

ATROPHY

By atrophy is meant wasting or diminution in size, of a cell or tissue. In the case of an organ it should mean wasting of its essential tissue, and this may be sometimes accompanied by actual increase in the size of the organ, owing to some other change. It is to be noted that an organ may be undersized as the result, not of atrophy, but of imperfect development; the term *hypoplasia* is applied to such a condition. Such hypoplasia is sometimes traceable to deficiency of endocrine secretion, for example the hypoplasia of the genital glands, which results from deficiency of the pituitary secretion at an early period of life. In some cases, however, no such cause can be found. Pathological atrophy has its prototype in the physiological atrophy of old age, which affects all the tissues, and notably the bones, lympoid tissue, and the sexual glands ; and though it is the case that some of the changes occurring in old age are the result of atrophy of the gonads, this atrophy in its turn cannot be explained. The cause of senile atrophy is of course merely part of the larger question as to the limited duration of life.

As regards the changes which occur in atrophy, there may sometimes be merely a diminution in the size without qualitative change. Specialised epithelial cells, however, tend to lose their special features or to become dedifferentiated, as may be seen in local atrophic changes in the liver and kidneys. Atrophy is not infrequently accompanied by accumulation of brownish pigment of lipoidal nature (p. 168). The term *brown atrophy* is applied to this condition, which tends to be more pronounced in the later years of life.

Causes of Atrophy :—*Defective Supply of Nutriment.* This may be produced locally by arterial disease interfering with the supply of blood to a part, when the interference is not of a degree sufficient to cause necrosis. The important elements of the tissue then undergo atrophy, and sometimes there is also a concomitant overgrowth of the connective tissue, the condition being then called *fibroid atrophy*. This is often well seen in the case of the kidneys, where small atrophic depressions result from narrowing of the lumina of the small arteries. When there is atrophy of the muscle cells of the heart wall, or of the walls of arteries the overgrowth of connective tissue becomes very marked, and this is probably to be regarded as of compensatory nature since it gives support and prevents dilatation. What may be called a *general atrophy* is seen in cases of starvation. The emaciation depends chiefly upon a using up of the fat of the adipose tissue but there is also a general wasting of the tissues. The various organs may thus become diminished in weight, the liver and spleen are markedly affected, the kidneys and heart to a less though distinct degree, whilst the central nervous system is only slightly affected. In the great majority of cases of wasting disease, however, such as malignant growths of the alimentary tract, chronic tuberculosis or suppuration, etc., a toxic element is concerned in the production of the wasting. Various degenerations may thus come to be associated with atrophy, and secondary anæmia is present, the latter condition being absent or little marked in pure cases of starvation. The term *cachexia* is often applied to a combination of wasting, anæmia and weakness.

Diminished Functional Activity. It is a general law that diminution in the katabolic processes leads to anabolism below the normal and thus to diminution in the size of cells. When the function of a part is in abeyance the blood supply also is diminished, and it might be supposed that this is the cause of atrophy. The converse condition of hypertrophy, however, is due to the increased metabolism and not to the accompanying hyperæmia, and accordingly it is likely that atrophy depends on diminished metabolism. This *inactivity atrophy*, as it is sometimes called, is seen when a gland, for example the pancreas, has its duct obstructed; its functional activity is thus stopped and it undergoes atrophic change. In a corresponding manner, tubules of the kidney undergo atrophy when their glomeruli are thrown out of action. The muscles around a joint which has been fixed for some time may undergo marked atrophy and the bones also may be affected. The changes in the muscles, however, occur sometimes so rapidly that, in addition to inactivity, a reflex trophic effect may be concerned. Unless such atrophy has gone on to an extreme degree the condition may be largely recovered from, when full functional activity is once more restored.

Interference with the Nerve Supply. This form of atrophy is seen where there is any destructive lesion of the lower motor neurons or their axons, the motor nerves; these lesions will be described later (p. 773). In this type, which may be called *neuropathic atrophy*, there is not only a simple wasting, but also more active degenerative changes in the nerve fibres and muscles. In the former the well-known Wallerian degeneration takes place, in which the myelin breaks down into fatty lobules, whilst in the latter, fatty degeneration also occurs, and this is followed by absorption of the sarcous substance and increase of the interstitial connective tissue (Fig. 83). That this form is different in nature from inactivity atrophy is shown by the 'reactions of degeneration' which are given by the muscles, and when these have undergone this atrophic change a complete return to normal is no longer possible. It should be mentioned that sometimes marked atrophy occurs also in the bones from the same cause. For example, in cases of infantile paralysis, the bones of the limb may become thin and light, and this appears to be due not simply to inactivity, but to a true trophic disturbance (Fig. 84). In a certain group of muscular atrophies, however, no lesion can be found in the neurons or in the nerves, and the term *primary myopathy* or *muscular dystrophy* is often applied (p. 854). In one variety the muscles become greatly shrunken, whilst in

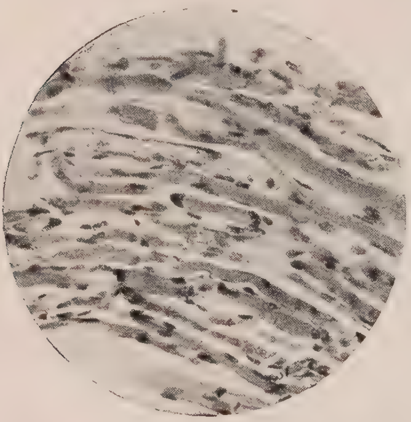


FIG. 83.—Atrophy of Voluntary Muscle from a case of Chronic Neuritis, with Increase of Interstitial Tissue. × 250.

another they are increased in size owing to extensive accumulation of fat between the atrophic fibres (Fig. 536). To this latter variety the term *pseudohypertrophic paralysis* is given.

Deficiency of the Endocrine Glands. The effects of this are seen mainly when deficiency occurs at an early period of life, so that the full development of the body is interfered with and thus hypoplasia results. This is especially seen in deficiency of the thyroid and of the anterior lobe of the pituitary (pp. 925, 932). A striking example of true atrophy in the adult, however, is seen in myxœdema due to thyroid deficiency. In this affection there occurs marked atrophy of the structures of the skin—hair follicles, sweat glands and sebaceous glands. And it is an interesting fact that restoration of structure and function may be produced by oral administration of thyroid.

Toxic Action. The best example of this is probably the wasting of the muscles in fevers. No doubt inactivity and interference with nutrition also play a part, but it is probable that the wasting represents chiefly a using up of proteins, as is indicated by the increased excretion of nitrogen. This increased protein metabolism, as will be shown in a later chapter, is one of the characteristic features of fever and is generally regarded as the result of toxic action, though the whole question is still somewhat obscure. Other tissues may suffer atrophy in a corresponding way, but in the organs the chief changes are of a more pronounced degenerative nature—cloudy swelling, fatty degeneration or actual necrosis of cells.

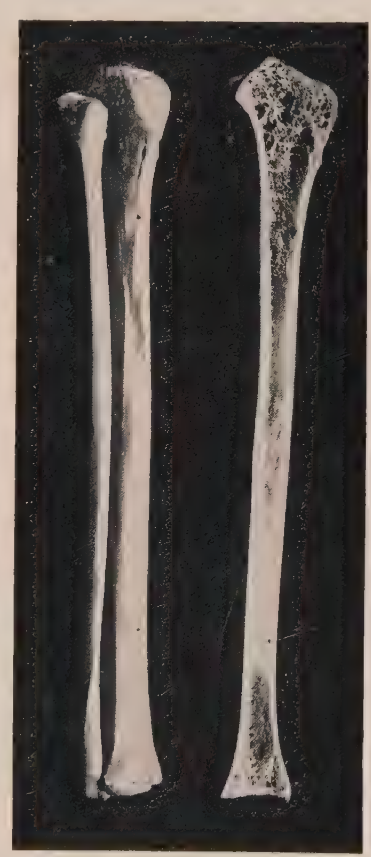


Fig. 84.—Tibia and Fibula from a case of long-standing Infantile Paralysis, showing marked Atrophic Change.

The tibia is shown also in section.

Finally, there is often described the form of *atrophy due to pressure.* This must be of a continuous nature, and it acts mainly by interfering with the blood supply and also the functions of a tissue. Thus atrophy of the organs may be brought about by pressure of simple tumours, cysts and the like. Even bone may undergo atrophy from such a cause, but in this instance it is not a case of simple wasting, but rather one of active absorption of the bone by cellular activity, osteoclasts being concerned in the process.

The above is merely a survey of the subject of atrophy, which will be illustrated further in connection with disease of the different systems. It will be clear from what has been stated that atrophy is in many instances a complex process and cannot be ascribed to any single cause. Analysis of atrophy is of high importance in clinical work.

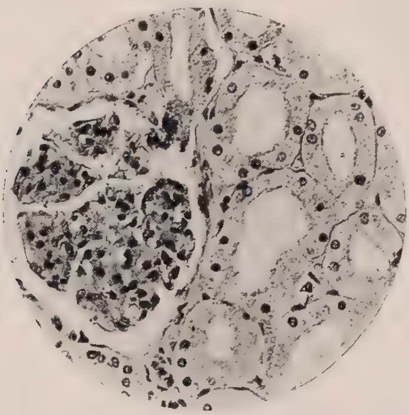


FIG. 85.—Section of normal Human Kidney, to compare with Fig. 86. × 250.

CLOUDY SWELLING

This condition, which is known also as albuminous or parenchymatous degeneration, may be regarded as one of the earliest indications of structural damage to the cell. The change tends to be most marked in specialised cells, e.g. those of the kidney and liver, muscle fibres of the heart, etc. The commonest causes are bacterial and other infections with fever—septicæmia, pneumonia, typhoid fever, etc., but it is produced also by various poisons such as carbolic acid, corrosive sublimate, etc., and it is a general precursor of fatty degeneration (p. 142) If the affected cells, say those of the liver, are examined in the fresh condition, they are found to be somewhat enlarged and more spherical than usual, and the protoplasm has a cloudy appearance owing to the presence in it of numerous small granules, which often obscure the nucleus. These granules are largely soluble in weak acetic acid and in weak alkalies and are generally regarded to be of protein nature. They may be accompanied by small droplets of serous fluid or of lipoids, and all stages to fatty degeneration may be met with. These droplets or globules

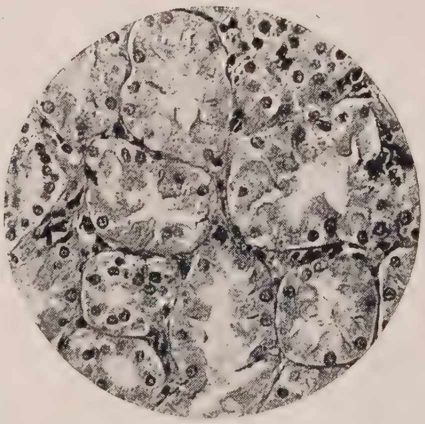


FIG. 86.—Cloudy Swelling of Tubules of Kidney, showing the Granularity and Projection of the Cells. × 250.

are often a prominent feature in the cells of the convoluted tubules in the kidney, and the free extremities of the cells are often broken off, so that the lumen contains granular material (Fig. 86).

It is to be noted that the appearances of cloudy swelling are much exaggerated when there is time for autolytic processes to occur after death; when the organs are examined at once they are much less marked. In fact we may say that the tissues as ordinarily obtained at a post mortem examination are quite unsuitable for the study of the finer histological details. The swelling of the cells, which varies in degree, is probably an osmotic phenomenon due to increased molecular content, from breaking down of the larger molecules. Much discussion has taken place as to the nature and significance of the granules, their formation being regarded by some as due to a process of aggregation of colloids preliminary to precipitation, whilst others regard the changes as in part of reactive nature or as indicating increased nutritional activity. It seems, however, justifiable at present only to say that they represent mainly a disintegrative or degenerative effect which may be followed by the appearance of fatty or other globules. Lorrain Smith and Rettie have shown that the earliest change in cloudy swelling occurs in the mitochondria, which lose their filamentous structure and form granules which come to stain like lipoids. They have found this to be the case in the action of a variety of poisons, and their results, which are in accord with other recent work, are of importance in demonstrating the first signs of damage to the cells. In the case of post mortem material many of the granules present do not give the reaction of lipoids, and they regarded these as being the result of autolysis. The relation of the granules soluble in weak acid to the lipoid granules is, however, not yet clear. In addition to fatty degeneration, cloudy swelling may be followed by actual necrosis of the cell with the usual nuclear changes. On the other hand, when recovery from the disease occurs, there is no

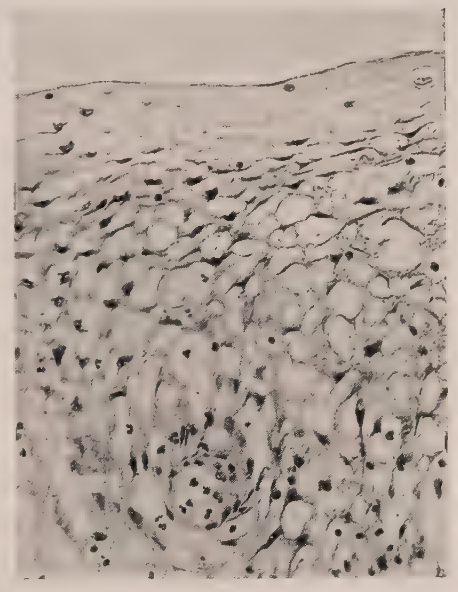


FIG. 87.—Serous or Dropsical Degeneration of Epithelial Cells, of Inflammatory Nature; the Cells are distended with rounded Collections of Fluid.

From a case of acute inflammation of the larynx. × 250.

doubt that the cells may resume their normal state. Organs in a state of cloudy swelling are usually somewhat swollen and of diminished consistence, and tend to have a pale pinkish and rather blurred appearance, sometimes compared to that of scalded or parboiled meat.

Closely allied to cloudy swelling is **serous** or **dropsical** degeneration, which often occurs when cells are acutely injured. It is really an œdema of cells, probably due to formation of smaller molecules and increased osmotic pressure in the cell protoplasm, with consequent absorption of fluid. The change is well exemplified in the skin epithelium in burns, and in acute infections such as anthrax and smallpox. The cells in such conditions become greatly distended with fluid (Fig. 87), and may actually burst; there is also accumulation of fluid between the cells. A similar dropsical condition of varying degree is common when cells lying free in a fluid undergo degenerative change.

FATTY CHANGES

Disturbances of the metabolism of fat form a very important subject in pathology. The terms *fatty degeneration* and *fatty infiltration* have long been in common use to indicate two different conditions. The former has been ordinarily accepted as meaning the accumulation of fat in degenerated or damaged cells, the latter as meaning an excessive accumulation of fat in normal metabolism, especially in the connective tissues and the liver. The distinction is important. The nomenclature, however, has become unsatisfactory in view of more recent work, which shows that at least most of the fat seen in fatty degeneration is infiltrated fat. Aschoff meets this difficulty by using the term ‘ fatty infiltration in damaged cells ’ to indicate the old fatty degeneration, and ‘ fatty infiltration of normal cells ’ to indicate the old fatty infiltration. We think it better to retain the old terms as meaning accumulation of fat in damaged cells and accumulation of fat in normal cells respectively. This leaves open the question as to whether all the fat in fatty degeneration is infiltrated fat. With this explanation we shall consider the two conditions.

Fatty Degeneration is a condition in which there is damage to cells which is accompanied by the appearance of droplets of fat in the cytoplasm. The fat, even in an advanced stage, tends to be in the form of minute globules which have little tendency to run together, or in other words constitutes a sort of coarse emulsion. The affected cells may be swollen but are usually not enlarged to any extent. In the fatty degeneration produced by phosphorus poisoning, however, the cells of the liver, for example, are considerably enlarged owing to the addition of fat to them. The fatty material mainly consists of the ordinary neutral fats—glycerol esters of palmitic, stearic, and oleic acid ; the last-mentioned is always present, and many of the microchemical tests depend on its non-saturated grouping. Free fatty acids may be present and various intracellular substances which are soluble in ordinary fat solvents and are ordinarily spoken of as lipoids. Of the lipoids the most commonly occurring and of widest distribution are cholesterol esters. These are considered later (p. 149).

The cells most frequently affected by fatty degeneration are those with specialised function, such as secreting cells, muscle-cells of heart, etc. (Figs. 88, 89); but whilst this is so, practically any cell in the body may be the seat of the change in certain conditions. For example, in phosphorus poisoning fatty degeneration is often very widespread, and may affect the endothelium of capillaries, connective-tissue cells, etc.

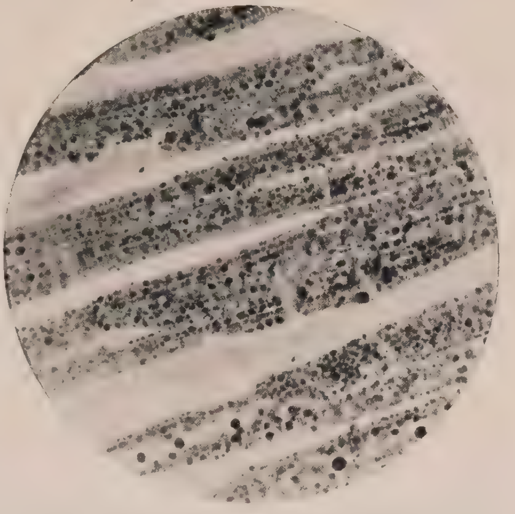


FIG. 88.—Fatty Degeneration of Heart Muscle, stained with Perosmic Acid.

Note the very numerous minute nodules arranged in rows; the transverse striation is well preserved. (Prof. J. Shaw Dunn.) × 400.

Tests for Fat. These depend partly on physical, and partly on chemical properties. The following are those most frequently used: (1) The fat can be dissolved out of the tissues by the ordinary fat solvents—ether, benzol, carbon disulphide, etc.; minute spherical spaces, in which the fat globules lay, are left, but the characteristic staining reactions are, of course, no longer given by the residue.

(2) Fat is stained black by a watery solution of perosmic acid. This depends on the reduction of the acid by the unsaturated olein and a black deposit forms, chiefly on the surface of the globules. The myelin of medullated fibres and also degenerated myelin are stained in this way, but the latter is less easily oxidised than

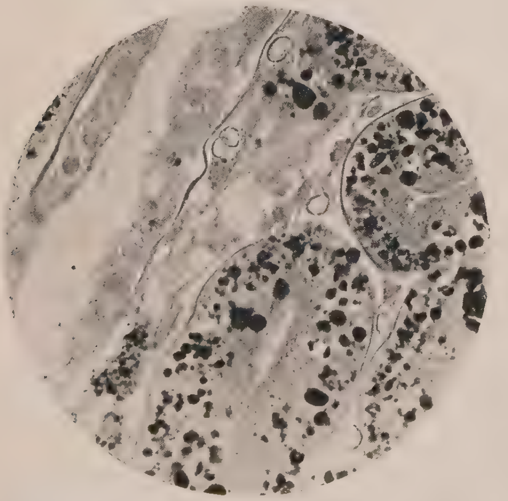


FIG. 89.—Fatty Degeneration of Tubules of Kidney, stained with Perosmic Acid. (J. S. D.) × 400.

the former. Accordingly, when treated for a time by an oxidising agent such as potassium bichromate (generally used as Müller's fluid), healthy myelin, owing to its having become completely oxidised, no longer reduces and is not stained by perosmic acid, while the degenerated myelin still reduces and is stained black. This is the basis of Marchi's and allied methods for tracing degenerated tracts in the central nervous system.

(3) Fat is readily coloured by certain aniline dyes of the azo series. These dyes, of which sudan III, scharlach-rot and fett-ponçeau are the most used, are chiefly reds and yellows, and their staining property depends on their extreme solubility in fat. The fat globules, in fact, come to be droplets of concentrated solution of the dye and thus appear coloured.

(4) Fat when hydrolysed by a weak acid is coloured by basic aniline dyes, e.g. gentian violet, as was first shown by Lorrain Smith. In this case the staining is due to the combination of the fatty acid split off with the coloured base of the dye. The same observer showed also that when fat is stained with Nile-blue sulphate, an aniline dye of the oxazine series, the results exemplify this principle along with that of (3). Some of the fat is coloured blue with the dye, and this is acid fat, the fatty acids combining with the oxazine base in the manner just explained. Neutral fat, however, is coloured a deep red, and in this case the explanation is the same as in the case of sudan III, namely, the red dye is extremely soluble in the neutral fat. The red substance is an oxazone base which is formed by oxidation from the oxazine when the salt is in a watery solution, and is a relatively inert substance. The method thus gives a picture of the proportion of neutral and acid fats present.

(5) Lorrain Smith found also that fats can be stained by Weigert's method for staining the myelin of nerve fibres. This method depends on a process of oxidation by bichromate; at a certain stage of the process the trioxide of chromium forms a link between the myelin and hæmatoxylin, and the combination results in the formation of a coloured lake, so that the myelin remains coloured after the rest of the tissue has been decolorised. Ordinary fat is less quickly oxidised than myelin, but if the process of bichromating fat is continued long enough, especially at a warm temperature, there comes a stage when a similar lake is formed with hæmatoxylin, and the fatty globules are stained. At this stage the myelin may be completely oxidised and no longer capable of being stained.

Lorrain Smith and Rettie have shown that lipoids and fats can also be mordanted by solutions of aldehydes, the mordanting process being effected by treatment at 37° C. for from one to two days. The sections are then stained by hæmatoxylin and decolorised by borax and potassium ferricyanide, the fatty globules remaining blue. They have found that in this method the lipoids and fatty globules met with in degenerations are more readily mordanted and stained than the stored fat of adipose tissue.

Naked-Eye Changes. An organ which is the seat of fatty degeneration becomes paler and of yellowish tint, in proportion to the degree of the change. When the degeneration is general the yellowish colour is diffuse, but when it is uneven in distribution a yellow mottling results. The latter is a marked feature, for example, in the fatty heart due to anæmia and also in the fatty degeneration of the kidneys secondary to nephritis. If the change be very marked the cut surface of the organ may be distinctly greasy in character. It must be recognised, however, that a considerable amount of diffuse fatty change may be present in an organ without distinct alteration in the appearance, especially when the organ contains much blood; and the true condition can be ascertained only on microscopic examination. Care should be taken in inferring the presence of fatty degeneration merely from the pallor of anæmic organs.

Fatty degeneration is usually regarded as implying a disintegration in part of the cytoplasm and thus a diminution of the functional capacity, but as there is always a reserve power the effect may be little apparent. A heart which is the seat of fatty degeneration may thus act fairly well in ordinary conditions, but it may suddenly fail when any strain is thrown on it. In pernicious anæmia the tubules of the kidneys may be in a state of marked degeneration without there being any distinct change in the urine. Cells in a condition of fatty degeneration may not be permanently damaged and the condition may be recovered from when the cause is removed.

Causes of Fatty Degeneration. These are very numerous, but they fall chiefly into two great groups, viz. (*a*) interference with nourishment and especially with oxygen supply, and (*b*) the action of various poisons. To these may be added a third, (*c*) interruption of the nerve supply to a part; this may be said to result in neuropathic fatty change in nerve and muscle.

(*a*) *Diminished oxidation* appears to have a close relation to the occurrence of fatty degeneration. Thus the change is of common occurrence throughout the organs in severe anæmias. It is specially marked in pernicious anæmia, and its distribution in certain situations suggests a relationship to diminished oxygen supply. Thus in the liver it occurs especially in the central zone of the lobules, while in the heart it is more marked in parts farthest from the arterioles (Fig. 330), that is, it is pararterial in distribution. Fatty degeneration occurs also in anæmia produced by hæmorrhage. Local fatty degeneration may be caused by interference with the blood supply by arterial disease; for instance in the heart, by narrowing of a branch of a coronary artery. It has also been produced in this way experimentally, e.g. in the liver by ligature of the hepatic artery. Further, it is met with in imperfectly nourished tissues, e.g. in tumours; in collections of desquamated cells, e.g. in catarrhal nephritis; in pus of old standing, etc., though in certain of these conditions the possibility of toxic action cannot be excluded.

(*b*) *Poisons* which produce fatty degeneration are of various kinds; they may be simple chemical substances of known constitution, or they may be bacterial or other toxins. Of the former, phosphorus, and chloroform are well-known examples, and have been largely employed in the experimental investigation of the subject. Such substances, though they may interfere with processes of oxidation, act chiefly as cell poisons. Then, again, the toxins of a great many bacteria produce fatty degeneration; in fact, it is the common result when cloudy swelling has lasted for some time. Thus it is frequent in septicæmias and in the various infective fevers—typhoid, smallpox, yellow fever, diphtheria, etc. It can be produced by the injection of diphtheria toxin, and this also has been used as a means of study.

The distribution is usually of a more diffuse character than that seen in the fatty degeneration of anæmia.

(*c*) *Lesions of Nerves.* When the continuity of a nerve is interrupted, the well-known Wallerian degeneration occurs in the distal segment, and the globules which are set free from the myelin give pretty much the reactions of the ordinary neutral fats, being stained by Marchi's method. The change is probably the result of an autolytic process which begins in the degenerating axons. Fatty degeneration may follow also in the associated muscle fibres.

Nature of Fatty Degeneration. The view of Virchow, according to which the change consists in a formation of fatty globules from the cell proteins, is no longer tenable. Largely owing to the work of Rosenfeld it had come to be believed that there are two main types of fatty degeneration. (*a*) The cells are damaged, e.g. by a poison such as phosphorus, and then there occurs in them an accumulation of fat which has been transported from the depots in adipose tissue ; there is thus an infiltration of fat in the damaged cells. Rosenfeld showed that this obtained especially in the liver and the result has been generally accepted. In accordance with this, it is to be noted that in a state of extreme emaciation little or no fatty change occurs in such a condition as phosphorus poisoning. (*b*) As a result of the condition which causes the fatty change, the fat which is in combination with protein, ' masked fat,' is set free and becomes detectable by ordinary micro-chemical methods. This process of liberating or unmasking fat is known as *phanerosis*. It was found to occur notably in the kidneys. Recent work by Dible and his co-workers, however, has led to contrary results. They have shown, for example, that in fatty degeneration of the heart muscle, in which phanerosis was believed to be the essential factor, there is an actual addition of fat to the fibres affected by the change ; and further this fat corresponds with the depot fat in having a lower iodine value than the fat of the normal heart muscle. They have also found evidence that transport of fat and infiltration are concerned in fatty degeneration of the kidneys. It is thus evident that in the organs mentioned the fatty change is chiefly, at least, an infiltration. It remains to be determined whether phanerosis plays any part and, if so, to what extent. Fatty degeneration has also been studied by modern histological methods and some facts may be given.

Observations on tissue cultures show clearly how readily the fat metabolism of cells is affected by their environment. Many cells in culture, when healthy and proliferating, contain minute globules of fat stainable by sudan III, but, when growth is less active or when the medium is not specially suitable, fatty globules become more numerous and of larger size. It is generally agreed that the mitochondria are composed of protein in combination with lipoid, and the earliest degenerative change has the appearance of being a splitting off of the lipoid, which comes to form a droplet stainable by stains for fats. Lorrain Smith and Rettie described this occurrence and concluded that both cloudy swelling and fatty degeneration began with destruction of mitochondria (p. 141).

Scott gave an account of similar changes in cells of the pancreas as a result of poisoning with phosphorus, the mitochondria forming minute globules which afterwards became agglutinated and fused. And Janet Niven, working in my laboratory, has obtained a similar result by study of the action of phosphorus fumes on the cells in tissue cultures. In all these cases it has been found that the mitochondria become altered and assume a granular form, and that the granules gradually come to give the reaction of lipoids or fats. It is not possible to pronounce definitely on the interpretation of the appearances described.

Fatty Infiltration. In this condition there is an increase of fat in the tissues which normally store fat, whilst there is no evidence of damage to the cells. These are chiefly the adipose tissues and the liver parenchyma, though in certain animals fat, accumulates also in the kidneys. Abnormal accumulation of fat in these situations might theoretically be due to an increased assimilation of fat or to diminished oxidation, or to both of these combined.

Fatty Infiltration of the Liver is an exaggeration of a normal process. The *foie gras* of the goose is a well-known example. It occurs in general obesity, but may be of marked degree in certain other conditions. The accumulation of fat usually begins and is greatest in the liver cells round the portal tracts (Fig. 90); thence it extends inwards, and in severe cases the whole lobule may be infiltrated. The fat appears first as a few small glubules which run together, and ultimately the cell becomes distended with a single large globule of fat, while the nucleus is flattened and pushed to one side. In extreme cases almost every liver cell is distended with a fat globule, the microscopic appearance coming almost to resemble adipose tissue. When there is great accumulation of fat the liver becomes much enlarged, greasy and of yellow colour. Such a condition is met with in chronic alcoholism, where apparently interference with the oxidation of fat occurs. It is seen also in some cases of pulmonary phthisis. The infiltration may be attended with cellular degeneration in these conditions.

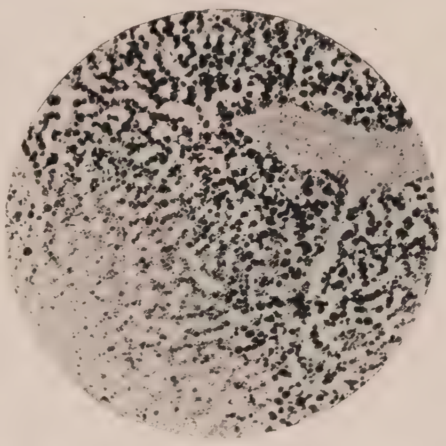


Fig. 90.—Fatty Infiltration of Liver, stained with Osmic Acid.

Note the large globules of fat especially at the periphery of the lobules. × 60.

Fatty infiltration of the liver may also be produced by metabolic disturbance. For example, Dible has shown that it results from starvation and in this case is due to a transference of fat from the depots of fat in the tissues. The amount in the liver roughly corresponds with the amount of depot fat, and when the latter becomes exhausted in the later stages the liver fat becomes greatly reduced. Carbohydrates are known to be necessary for the oxidation of fat and the accumulation of fat in the liver in inanition may thus be the result of carbohydrate deficiency. In this way too the ketosis with presence of acetone bodies in the urine occurring in such states may have its explanation. The presence of excess of fat in the liver found at post-mortem examinations may accordingly simply depend on a state of malnutrition before death. The part played by infiltration in 'fatty degeneration' has been dealt with above.

Obesity or excessive fat in the connective tissues occurs from excess of fat and carbohydrates in the diet, especially when this is associated with want of exercise. But in addition there is a habit of body which tends to obesity, though the nature of this cannot be explained. It is further to be noted that this tendency may be acquired after passing through a severe illness, especially typhoid fever. In this connection it is suggestive that certain of the endocrine glands have an influence on the storing of fat. Deficiency of pituitary secretion in early life leads to adiposity, along with failure in sexual development, and there is evidence that some forms of obesity in the adult are due also to hypopituitarism. So also in sporadic cretinism, due to thyroid deficiency, there occur irregular accumulations of fat in the subcutaneous tissue.

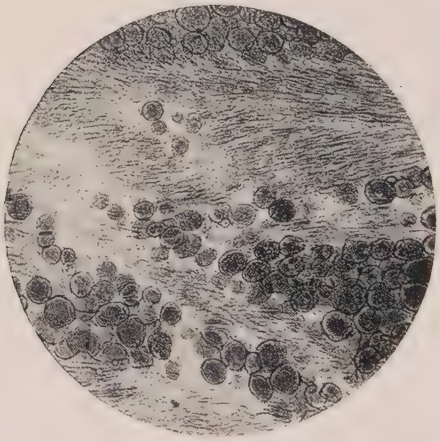


Fig. 91.—Fatty Infiltration of Cardiac Muscle.

Note oval fat cells between the muscle fibres (stained with sudan III). × 60.

Fatty Infiltration of the Heart is essentially a local adiposity or lipomatosis of the epicardial tissue, though it is not always proportionate to the amount of fat elsewhere, being sometimes well marked when there is comparatively little obesity. The fat extends along the lines of connective tissue through the heart wall, and leads to atrophy of the muscle fibres, and consequent weakening of the wall (Fig. 91).

Lipoidal Degeneration and Infiltration. In recent years it has come to be recognised that in addition to the changes just described, in which the ordinary neutral fats are concerned, accumulations of lipoids take place in the tissues in various pathological conditions. The lipoids are of considerable variety and apparently often occur as mixtures along with fats. The most important of them is a substance to which the name *myelin* or *myelin fat* has been given on account of its resemblance to the myelin of nerve fibres, and which has been shown to consist mainly of *cholesterol esters*, though other substances are associated with them. Myelin is anisotropic or doubly refracting, being in a fluid crystalline condition, and thus can readily be recognised by means of the polarising microscope (Fig. 92); when brought into contact with water, the globules assume various forms and send out narrow processes, forming the so-called myelin figures. It is usually stained a yellowish colour, less deeply than ordinary fat, with sudan III; and it is rendered black, or at least grey, with osmic acid, the variations probably being due to admixture of other substances. It must, moreover, be noted that the doubly refracting property is possessed by other substances in addition to cholesterol esters, e.g. phospholipins, fatty acids, cholesterol dissolved in fats, etc. And further, some of the doubly refracting lipins do not undergo the physical changes in water mentioned above.

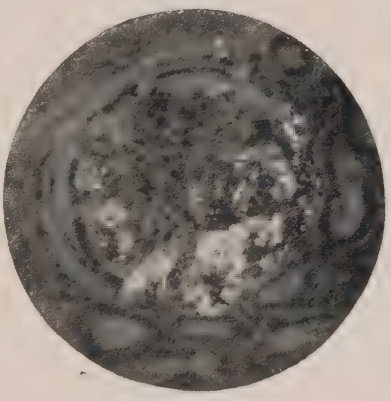


Fig. 92.—Myelin Fat in Glomerulus of Kidney in a case of Nephritis.

It has been photographed by light which has passed through crossed Nicol's prisms and is brightly illuminated owing to its doubly refracting character. (J. S. D.) × 200.

Cholesterol fat is normally present in the cells of the adrenal cortex in the form of small globules, and becomes increased in amount in certain conditions, especially where there is an increase of the cholesterol content of the blood. In fact, the adrenals seem to remove from the blood and store cholesterol fat pretty much as the liver stores ordinary fat. The former is normally present also in the interstitial cells of the testis and ovary. When an animal is fed with cholesterol dissolved in oil, an ester is formed in the process of absorption from the intestine, and then the normal stores of ester become increased. Not only so, but ester is also deposited in various organs, chiefly within histiocytes, and notably in the intima of the aorta, where it may form atheroma-like patches. Excess of cholesterol in the blood occurs in obesity, pregnancy, hydræmic nephritis, diabetes and obstructive jaundice; and it is interesting to note that in the two last-mentioned conditions, localised deposits of esters may occur in the cutis, giving rise to slightly raised yellowish patches—the condition known as *xanthelasma*. In nephritis of the hydræmic type (p. 662), associated with increase of the cholesterol content of the blood, there is often a large amount of doubly refracting fat both in the tubules and in the interstitial tissue of the kidney ; and globules are present in the urine both in casts and also in the free state.

Cholesterol fat is often deposited in the tissues in connection with local lesions, apart from any increase in the blood. It is found in various chronic inflammations, e.g. in chronic mastitis, in the region of chronic abscesses, in certain inflammatory exudates in the lungs, etc. It is often contained in large rounded phagocytic cells, which have a vacuolated appearance owing to its occurring in droplets ; the cells are often spoken of as foamy cells (Fig. 51). In the wall of the gall-bladder too it is not infrequently deposited, first within the cells of the sub-mucosa ; the deposits may come to form small spots visible to the naked eye, giving rise to the so-called ' strawberry gall-bladder (p. 623). The deposit of cholesterol fat in the tissues has a close resemblance to the ordinary fatty changes and like them occurs in both healthy and damaged cells. And just as occurs in calcification (p. 171), the deposit is mainly due to local tissue changes, though sometimes as the result of excess in the blood.

In certain cases where the cholesterol content of the blood is much raised, doubly refracting cholesterol fat may be deposited in the *spleen* to such a degree as to cause its enlargement. This is especially met with in some cases of diabetes and in obstructive jaundice. There are also affections of unknown etiology such as Gaucher's disease and Niemann's disease, in which there is a disturbance of the lipoid metabolism and lipoids are stored in enormous amounts in the spleen and other parts of the reticulo-endothelial system (p. 499).

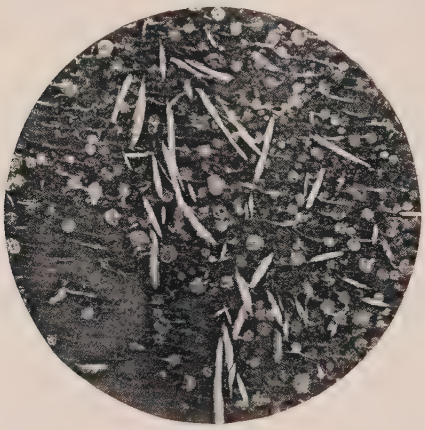


Fig. 93.—Spindle-shaped collections of Cholesterol Crystals and Granular Cells in degenerated tissue. × 80.

Cholesterol is met with also in the uncombined state, in the form of rhomboidal plates often with a deficiency at one angle. It occurs in conditions somewhat similar to those just mentioned, and may be abundant in old collections of pus, in dermoid cysts, and in long-standing collections of fluid, e.g. hydrocele fluid. When the tissues are embedded in paraffin, the cholesterol is dissolved out, and the spaces which contained it may appear as spindle-shaped clefts, often with giant-cells around them. Cholesterol is also an important constituent of gall-stones and one type of stone is composed of it in practically pure form.

Lipœmia. The term indicates an increase of lipins in the blood plasma.

The subject is a very complicated one as it involves fats, lipoids and phospholipins; these are often increased together but in varying proportion. Lipæmia has been observed in a variety of conditions such as chronic alcoholism, nephrosis, experimental anæmia, starvation, etc., and factors such as diminished oxidation, increased transport of fat from the tissues, etc., are concerned. The subject is, however, imperfectly understood. The increase would appear to be on the part of lecithin and cholesterol compounds as well as glycerol fat. It is in diabetes that lipæmia reaches its highest degree, and in some cases a milky layer of considerable thickness may form on the surface of the blood. The total amount of lipins may in exceptional cases be as high as 15 per cent. or even more, of the plasma. In this disease there is a deficiency in the metabolism of fat with formation of acetone bodies (p. 926), but the cause of the excessive lipæmia occasionally met with is unknown. A deposit of cholesterol esters may occur in the cells of the reticulo-endothelial system, in the spleen and liver.

AMYLOID OR LARDACEOUS DEGENERATION

This is the most important example of a degeneration which does not affect cells directly but formed elements, especially fine connective-tissue fibrils in relation to blood vessels. The affected elements become swollen, translucent and highly refractile in appearance, and present certain definite staining reactions. It was, in fact, the staining reactions which amyloid material gives with iodine, which led to the original view that the substance was a carbohydrate; hence the name. It is now known that amyloid is of protein nature. The change occurs in various internal organs and its distribution is specially related to capillaries and small arteries. In the former it affects the sub-endothelial tissue fibrils, and the swelling which results has two effects, viz. (*a*) enlargement or thickening of the capillary as a whole, and (*b*) diminution of its lumen. The former may produce atrophy of the adjacent cells by pressure, e.g. in the liver (Fig. 94); whilst the latter interferes with the blood supply and may lead to secondary results. In arteries the change usually begins in the fine connective tissue of the media; this leads to atrophy and disappear-

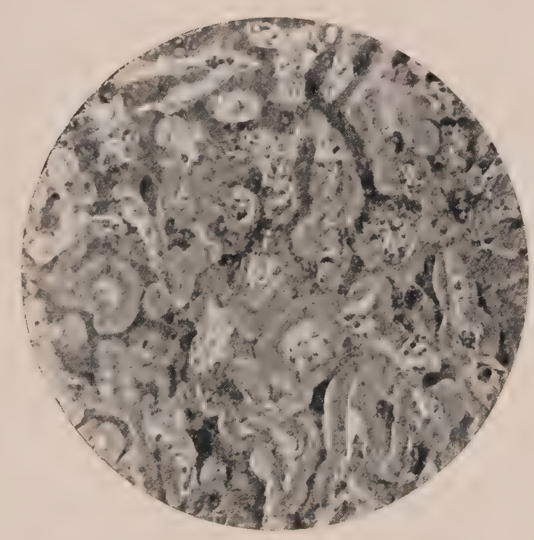


FIG. 94.—Amyloid Degeneration of Liver.

The pale homogeneous bands represent amyloid substance. The liver cells, stained more deeply, are seen in process of atrophy. × 250.

ance of the muscle and elastic fibres, and ultimately the coat has a homogeneous and structureless appearance. Amyloid degeneration often starts in the minute arterioles in organs, and thence spreads forward to the capillaries and backward to the larger arteries ; this distribution of the change may be well seen in the case of the kidneys. In later stages even the walls of veins, especially the intima, may be affected in a similar way, as may be seen in the branches of the portal vein in advanced amyloid disease of the liver. In addition to vessel walls, amyloid disease sometimes affects basement membranes, e.g. of the tubules of the kidneys, and also the delicate reticulum of lymphoid tissue.

Staining Reactions.

(*a*) Amyloid substance has a special affinity for iodine, and is stained deeply by it. A watery solution of iodine is, accordingly, of great service in detecting the presence of amyloid at a post-mortem examination. The amyloid portions are stained a deep brown colour and stand out prominently. In applying the test, it is important to select a part free from congestion, as any blood becomes slightly darkened by the iodine. In microscopic sections stained with iodine and examined in the usual way by transmitted light, the amyloid substance has an orange tint, whilst the rest of the tissue has a greenish-yellow colour and somewhat granular appearance. If, on the other hand, the light from the mirror is entirely cut off, and the section is illuminated merely by the light falling upon it, then the amyloid substance appears of a deep brown colour on a pale background, this result corresponding with what is seen on naked-eye examination.

(*b*) With gentian violet, methyl violet and certain other basic stains, the amyloid substance gives a metachromatic reaction, assuming a somewhat reddish tint, whilst the other parts are more of a violet tint. The contrast between the two becomes emphasised when the section is treated with weak acid.

(*c*) Amyloid substance when treated with iodine and afterwards with sulphuric acid, may assume a bluish-green colour. This reaction, however, is somewhat inconstant and is not much used. It is most frequently given by amyloid in the spleen.

Of these reactions, the metachromatic reaction with basic aniline dyes is the most constant and most reliable. It is believed that the simple reaction with iodine depends on a physical process of adsorption, whereas that with methyl violet is mainly of a chemical nature and depends on the chondroitin-sulphuric acid. It may be noted also that when amyloid tissues have been kept for a considerable time in preservative, they may fail to give the reaction with iodine, while they stain well with methyl violet, etc.

(*d*) *Congo Red.* This dye was introduced as a stain for amyloid by Benhold. He recommended its use in a 1 per cent. watery solution, the tissues being afterwards decolorised by weak sodium carbonate solution and 80 per cent. alcohol. By this method an almost elective stain of amyloid can be obtained. The method is applicable to paraffin sections.

Congo red when introduced into the circulation *intra vitam* is fixed by amyloid material, and if the latter is abundant it disappears more readily than in ordinary conditions. Benhold recommended the intravenous injection of 15 c.c. of a 0·75 per cent. solution of Congo red, the amount in the serum being afterwards tested by taking samples of the blood at varying intervals. In a normal individual 10–30 per cent. of the dye disappears within an hour, but if a considerable amount of amyloid is present, 40–60 per cent. may disappear. This method when used as a test for amyloid is of quantitative nature and the results must be interpreted accordingly; for example, disappearance of the dye is most rapid in cases of extensive amyloid disease of the liver.

Structural Changes and Distribution. Organs affected with amyloid disease become, as a rule, increased in size and firmer in consistence, whilst the specific gravity also is increased. The affected tissue on section shows a somewhat translucent or waxy appearance and contains little blood. An amyloid liver, for example, is firm and elastic; and its smooth surface and rounded margins can often be palpated during life. The change usually starts in the capillaries in the intermediate zones of the lobules, and may ultimately become so extensive that the greater part of the organ is constituted by amyloid substance (Fig. 95). Even when extensive, amyloid disease of the liver does not usually give rise to ascites.

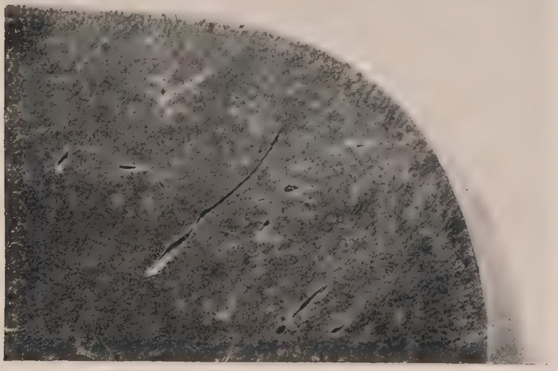


Fig. 95.—Section of Amyloid Liver, showing Naked-eye Appearances.

The darker and more homogeneous parts represent the amyloid substance. (Natural size.)

In the spleen there are two main types of amyloid. In one, the Malpighian bodies chiefly are affected, these being changed into somewhat translucent globules resembling boiled sago-grains; hence the term ‘sago-spleen’ (Fig. 96). In the other type, the diffuse form, the change affects the reticulum of the pulp and walls of the venous sinuses; and, accordingly, owing to the greater extent of the disease, the spleen becomes considerably larger in this form. Like the liver the spleen when amyloid is firm and may be palpable during life.

In the kidneys the disease brings about important secondary changes. It is associated with hypercholesterolæmia, and the lipoids in excess in the blood pass through the walls of the glomerular capillaries and are absorbed by the tubular epithelium. In this way, the kidneys are enlarged and paler than the normal, while the cortex shows yellowish mottling owing to the fatty change. The condition is often associated with marked albuminuria and œdema, and is known as the 'amyloid type of nephrosis.'

These are the organs most frequently affected by amyloid disease, but it may have a widespread distribution. It may be present in the mucosa of the stomach and intestines and lead to an anæmic condition with atrophic change. Here again, corresponding structures are affected, viz. arterioles and capillary walls. Amyloid disease may occur in the adrenals, thyroid, etc., and is not uncommon in lymphatic glands. It is occasionally met with also in the heart wall, most frequently in the right auricle, where amyloid patches underneath the endocardium may be detected by the iodine test. The nervous system, however, is never affected.

We have said that amyloid substance leads to atrophy of cells by pressure of the swollen capillaries and necessarily also interferes with the blood supply; but notwithstanding the presence of a considerable amount of amyloid, the disease may not lead to any detectable effect on the function of an organ. Amyloid disease of the renal vessels at an early stage often causes polyuria, the urine being of low specific gravity and containing little or no albumin; but at a later period oliguria and marked albuminuria develop in association with the lipoid accumulations in the tubules, as mentioned above. In the case of the intestine, amyloid disease is often attended by watery diarrhœa, possibly due to increased permeability of the capillary walls, though this is not certain.

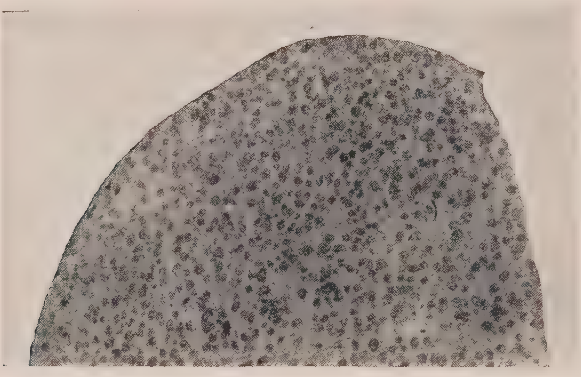


FIG. 96.—Amyloid Spleen of Sago Type, showing the affected Malpighian Bodies. (Prof. M. J. Stewart.)

Causation. The causes of amyloid disease are mainly three in number :—

(*a*) *Chronic Suppuration.* Amyloid disease was formerly a fairly common result of long-continued suppuration in bones, but since the introduction of modern methods of surgical treatment, it is now comparatively rarely produced in this way. It is not uncommon as a result of long-standing empyema in children.

(*b*) *Tuberculosis,* especially when it is attended by much caseation or suppuration, e.g. such as occurs in caseating lung tubercle, or in bone tubercle with cold abscess.

(*c*) *Syphilis.* As a rule it is met with fairly late in the tertiary stage of the disease; it occurs occasionally also in the congenital form.

Apart from these three main conditions, amyloid disease is rare. It has been found, however, in some cases of lymphadenoma, and in some cases of rheumatism (Beattie), where other causes could be excluded. It is stated to be sometimes due to dysentery, chronic malaria, and even to malignant disease. We must always bear in mind, however, that in such cases it may possibly be the result of syphilis, although no other manifestations of the disease may be found.

It is to be noted that in the three main conditions definitely known to produce amyloid disease, organisms are present, and also that their action extends over a relatively long period of time; how long a period is necessary to produce the change cannot be stated, but we have seen marked amyloid disease apparently produced within three months by acute pulmonary tuberculosis. It is possible that amyloid substance may undergo some absorption when the cause has been removed, but in view of the nature of amyloid this must be a relatively slow process. It has been shown, however, that amyloid, the result of suppuration produced experimentally in animals, may undergo absorption when the pus has been removed and healing of the abscess has been effected.

Nature of Amyloid. As has been said, amyloid is of protein nature, and is a relatively resistant substance. It can be digested by trypsin though more slowly than most proteins, but it is little affected by peptic digestion. It is soluble in alkalies. The work of Krawkow, which has been confirmed by others, showed that it corresponds in composition with a nucleo-protein and is really a combination of chondroitin-sulphuric acid and a protein. This acid is an important normal constituent of cartilage, and has been found also in parts rich in elastic tissue, e.g. in the aorta. It is difficult, however, to bring these facts into relationship with the pathology of amyloid, as it is not possible to attribute the large amount of chondroitin-sulphuric acid, which may be present in severe cases, to actual destruction either of cartilage or elastic tissue, e.g. in the lungs; and, furthermore, the amount of actual destruction of tissue in some cases of syphilis may be relatively small. Further, it has not been found possible to produce amyloid disease by injecting salts of chondroitin-sulphuric acid, or tissues containing it, into animals (Wells).

Amyloid disease has been produced experimentally in rabbits and fowls by injecting bacterial cultures, especially of staphylococci, but positive results are obtained only in a certain proportion of cases. Amyloid substance has been found to appear sometimes in horses used for the production of diphtheria antitoxin. Mice also are liable to amyloid disease, and may suffer from it when they are rendered tuberculous; it has been observed in them also when malignant tumours have been transplanted. It has been shown that repeated parenteral injection of foreign proteins in mice may lead to deposition of amyloid in organs. Nutrose, a caseinate, has been found to be specially effective as was first shown by Kuczynski; he also found that amyloid change could be induced by feeding mice with cheese. The earliest changes are best studied by intra-vitam staining with congo-red. Letterer considers that increase of globulin in the blood, which is noted in such experiments before amyloid appears, is an important factor in its deposition. The pathology of amyloid disease is, however, far from being understood. It may be added that the metachromatic reaction given by amyloid seems to depend upon the chondroitin-sulphuric acid.

Localised Amyloid. Amyloid change has been observed in the neighbourhood of abscesses, and in the lymphatic glands in relation to a suppurative area, whilst it was absent in other parts of the body. This is clearly an example of the direct effect of the concentrated toxins on the tissue elements. Amyloid occurs sometimes also in small connective tissue growths in the larynx, bronchi and the nasal septum, the change affecting the vessels and the connective tissue fibres. It is supposed that in this instance, the amyloid substance is due to the absorption of chondroitin-sulphuric acid from the cartilage in the vicinity. The structures known as *corpora amylacea* (p. 157) have nothing to do with amyloid proper.

HYALINE DEGENERATION

The term 'hyaline' is used in a general descriptive manner to indicate a somewhat homogeneous or glassy appearance presented by tissue elements, and thus it does not indicate a specific substance. Various tissues and cells may be altered in this way, but the most important form of the change is that which occurs, like amyloid change, in connective tissue fibres and in the walls of blood vessels. It is often known as *connective tissue hyaline*. The affected fibres become swollen, homogeneous in appearance and somewhat refractile, and the substance formed, which is of protein nature, is comparatively resistant to solvents. It is usually oxyphile in reaction and does not give the reactions of amyloid. The change is of common occurrence in the arterial system, notably in the small arterioles in essential hypertension, though also apart from this condition. Its important effects will be described later. It is met with also in lymphatic glands in conditions of chronic inflammation, and is not uncommon in certain forms of tumour, both in the stroma and in the walls of blood vessels. Although it is mainly the finer fibrils which become hyaline, a similar change may occur in coarser bands of connective tissue, e.g. in old scars and in various chronic inflammatory conditions.

Some other conditions to which the term 'hyaline' is applied in a descriptive way may be mentioned. Hyaline material may be formed, for instance, from the elements of the blood in thrombi. Fused and altered blood platelets have a hyaline appearance, fibrin may become condensed and of similar aspect, and red corpuscles may form so-called hyaline thrombi in capillaries. In inflammatory conditions, hyaline material sometimes arises from fusion of exudate with the stroma elements ; this process may be seen, for instance, in chronic tubercle. Droplets of homogeneous and somewhat refractile appearance occurring within cells are often described as hyaline, and such are found both within epithelial and connective tissue cells. 'Hyaline droplet change' is often a prominent feature in the kidney epithelium in nephritis (Fig. 411). Lastly, it may be mentioned that delicate transparent casts met with in the urine in nephritis are ordinarily known as hyaline. These examples are sufficient to show how heterogeneous is the group of substances to which the term has been applied.

Corpora Amylacea. Under this term are included a number of rounded or oval hyaline structures, which may stain deeply with iodine, hence the name. They sometimes show concentric lamination and not infrequently undergo calcification. Such structures are met with in a variety of situations and they cannot be regarded as all of the same nature. They are often a prominent feature within the acini of the prostate in the later years of life ; they occur also in old infarctions in the lungs, in old blood clots and sometimes in tumours. The presence of structures of this nature in the nervous system is very common ; they are met with in chronic degenerative lesions, and are sometimes numerous in the region of old softenings and hæmorrhages. They vary greatly in size, the smallest being spherical and homogeneous, and these usually stain deeply with hæmatoxylin. They appear to form simply by a separation out of organic material in globular form in the intercellular spaces, but their real composition is not known. So far as is known they are of no importance except as a manifestation of the degenerative condition with which they are associated, and in themselves give rise to no effects.

MUCOID DEGENERATION

Under normal conditions mucin is produced both by the epithelial cells of mucous membranes, glands, ducts of glands, etc., on the one hand, and by connective tissue cells, notably in the tissues of the fœtus, on the other hand ; and the mucin met with in excess in pathological conditions is correspondingly of two main types—*epithelial mucin* and *connective tissue mucin.* The mucin in pathological states is not a single substance, but represents a group of substances which have the common physical property of imparting a slimy character to fluids, and which differ somewhat in their chemical reactions. Mucins are glyco-proteins, being composed of protein and a carbohydrate radical, glucosamine, and on their being treated with hydrochloric acid, the glucosamine usually reduces Fehling's solution; one variety, viz. paramucin, gives this reaction directly. They are as a rule precipitated by acetic acid and by alcohol, but the pseudomucin of ovarian cysts is not precipitated by the former. Mucins are usually somewhat basophile, and often give a metachromatic reaction with toluidin blue, being stained a reddish purple; but variations in staining reaction, corresponding with chemical constitution, are met with.

Increased formation of *epithelial mucin* is usually the result of increased secretion rather than of cell degeneration, as is well seen in catarrhs of mucous membranes. When a catarrhal inflammation has become chronic there is often an increase of mucin-forming cells; this is noteworthy in chronic gastric catarrh and probably represents a change to a more resistant form of epithelium. Cysts containing mucoid fluid may be formed by obstruction of ducts, and here also the mucin is mainly produced by secretion. A similar statement holds in the main with regard to cystic tumours, notably the multilocular cystoma of the ovary which contains pseudomucin, though degenerated cells undergo a mucoid swelling and merge with the contents. The so-called colloid cancer ought really to be called mucoid cancer; in this form of growth the epithelial cells actively form mucin and rapidly undergo degeneration and become lost in the homogeneous substance. The latter is mucin in an inspissated state and there is little doubt that the growth takes origin from mucin-forming cells.

Mucin-forming connective tissue, usually called *myxomatous tissue*, is characterised by the presence of a clear mucin-containing matrix between the cells, whilst the latter have a somewhat stellate form with branching processes and there are few collagen fibrils. Such tissue is a fairly common constituent of various tumours (Fig. 111), and intermediate stages between it and merely œdematous connective tissue are met with. Granulation tissue may sometimes present a myxomatous appearance, apparently the result of chronic œdema and altered nutrition. The term *myxœdema* was applied to the disease resulting from deficiency or absence of the thyroid secretion, on account of the altered condition of the connective tissue of the skin and other parts, the tissue becoming swollen and somewhat gelatinous. It has been found that there is an increase of the mucin in the connective tissue in the early stages of the disease, but later the amount may not be above normal. When the thyroid is removed experimentally in animals, e.g. monkeys, the connective tissue becomes swollen and contains considerable excess of mucin.

Colloid Degeneration. The term colloid means glue-like, and may be applied to stiff translucent material; but, like 'hyaline,' it is only a descriptive term and connotes nothing of a definite chemical character. For a long time it has been applied to the secretion of the thyroid which contains the characteristic substance iodothyrin (p. 929), and when the thyroid becomes enlarged owing to the accumulation of secretion, the term *colloid goitre* may be conveniently used. In certain conditions the thyroid secretion becomes more fluid or serous in character and stains less deeply with acid dyes. Unfortunately, the term has been applied to substances which have nothing to do with thyroid secretion, and which in fact possess no properties to justify a special name. The material in 'colloid' cancer has, as we have stated, the properties of concentrated mucin, and that in 'colloid' ovarian tumours belongs to the same group of substances. Other protein-containing fluids may become inspissated and assume a glue-like character. The colloid cysts in the kidneys and the colloid casts in the tubules in chronic nephritis are probably produced in this way, with the addition of epithelial products (Fig. 97). These casts are of larger size than the hyaline casts occurring in the more acute stage, and, unlike the latter, are readily stainable in sections, having an affinity chiefly for acid dyes, to a less extent also for basic.

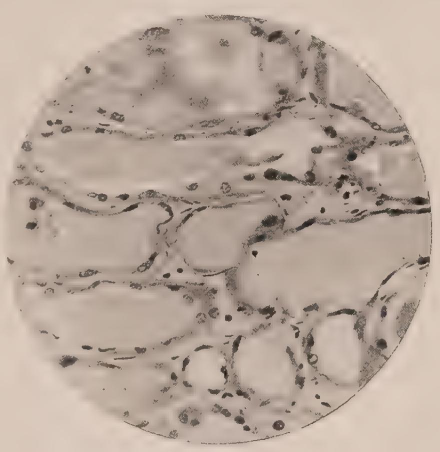


FIG. 97.—Colloid Casts in Kidney, seen as Homogeneous Material within the Tubules; from a case of Chronic Nephritis. × 250.

PIGMENTARY CHANGES

Pigments are deposited in the tissues in a great many abnormal states, and may produce naked-eye or microscopic changes, or both. In part they are formed within the body—*endogenous* pigments; in part they enter the body from the outside—*exogenous* pigments. Of the former, the two main varieties are melanin and derivatives of hæmoglobin, though there are some others less important.

(A) ENDOGENOUS PIGMENTATION

(1) Melanin Pigmentation. The pigment of the skin may show variations, in the direction either of increase or decrease. A general increase occurs in Addison's disease, especially in the parts exposed to light and in those normally pigmented; and there may also be pigmentary deposit on the inner surface of the cheeks on a line corresponding to the junction of the teeth, and on the sides of the tongue, the position of deposit being apparently determined by irritation. In the skin the pigment is in the form of very fine brownish granules in the deeper layers of the rete Malpighii, and is present also as coarser granules, chiefly within cells or chromatophores in the underlying cutis, the appearance and distribution resembling those in the negro's skin. There is little doubt that the pigmentation in Addison's disease represents an increase of normal pigment, though this has been questioned by some. Pigmented patches occur on the skin in *chloasma*, a condition of obscure origin; sometimes it is apparently due to uterine disorder and sometimes related to pregnancy. In this connection there is the interesting fact that in pregnancy pigmented parts may become of deeper tint. Areas devoid of pigment occur in the condition known as *leucoderma*, and these may be attended with increase of pigment in the intervening parts; the causation of the condition is not known. Irregular pigmentation of the skin is of common occurrence in chronic arsenical poisoning. The whole question of pigment metabolism in the skin is obscure, but it is known to be affected by a variety of influences, such as exposure to light, irritation, and increased vascularity, action of endocrine glands (at least the adrenals) and nervous changes. Melanin pigmentation is to be distinguished from that resulting from the deposit of blood pigments, where there has been escape of red corpuscles, e.g. in purpuric and erythematous conditions, etc. And in ‘bronzed diabetes’ also, the colour of the skin is chiefly due to deposit of hæmosiderin in the cutis, notably around the sweat glands (p. 166).

Melanin pigment is formed in large amount in the melanotic tumours which arise from pigmented moles and warts on the skin or from the pigmented coats of the eyeball, and most analyses have been carried out on the pigment from such tumours. There is no doubt that the melanin is the result of the metabolic activities of the cells and is not derived from hæmoglobin. It is a very stable substance and is resistant to acids and other reagents. It can, however, be dissolved by strong alkalies, and it is bleached by powerful oxidising agents such as potassium permanganate. The urine of patients suffering from extensive melanotic growths often contains a melanogen which, on exposure to the oxygen of the air, assumes a dark brown colour, and a similar condition of the urine is produced when melanin is injected into animals. Iron does not appear to be a constituent of melanin, most specimens of the pigment being found to contain little or no iron; and it is likely that any iron found may have come from blood pigment present with the melanin. Melanin is known to be related to the aromatic compounds such as tyrosine, phenylalanine, and tryptophane—substances from which pigments can be formed by oxidation. It is worthy of note that adrenalin belongs to the same group, and from it also pigment can be formed by oxidising enzymes. This fact is suggestive in connection with the pigmentation of the skin in Addison’s disease, due to adrenal deficiency, and it has been supposed that precursors of adrenalin, not being transformed into adrenalin as normally, accumulate in the skin and are there oxidised into pigment. Other results with regard to the relation of adrenalin to melanin support this view, but it cannot be regarded yet as fully established.

The fact that various aromatic compounds can be oxidised by enzymes to form pigments has been applied by Bloch to show the cells which produce such oxydases. Thus, using di-hydroxy-phenylalanine, now ordinarily known as 'dopa,' he has shown that certain cells in skin oxidise this substance by means of an enzyme like tyrosinase and become blackened in consequence; these are 'dopa-positive.' It is likely that the cells in the skin which give a positive reaction are producers of melanin and may thus be called melanoblasts. Such are certain pigment-holding cells in the basal layer of the *rete Malpighii* which are specially related to nerve terminations. (p. 250). The other cells of the epidermis react negatively, even though they may contain pigment. Pigment-bearing cells in the cutis do not give a positive reaction and may thus be called melanophores; they are usually histiocytes which have merely taken up melanin. Leucocytes of the myeloid series give a positive dopa reaction, but with this exception recent work shows that the reaction is peculiar to melanoblasts. Raper has shown that dopa may be formed from tyrosine by oxidation with tyrosinase and that by further oxidation and other processes a melanin is produced. Melanins evidently vary in their composition but it seems established that they are formed from colourless precursors or melanogens by processes of oxidation within cells possessing the necessary oxydase.

Melanosis coli. This is a fairly common condition occurring in the large intestine and characterised by areas with varying degrees of greyish to black pigmentation of the mucosa. The pigment is a melanin which is mainly contained within rounded cells in the mucosa; it is absent from the epithelial cells. The condition is commonest when there has been intestinal stasis or chronic obstruction, and it is now recognised to be the result of excessive protein putrefaction. Aromatic products thus resulting are absorbed and oxidised by the cells in the mucosa to form pigment. In accordance with this view the cells containing pigment are found to be dopa-negative, that is, are not melanoblasts.

Ochronosis. This is a very rare condition in which cartilages, capsules of joints and other soft tissues assume a dark brown or almost black colour, owing to the deposit of pigment. The pigment has been found to belong to the melanin group. In a pretty large proportion of cases of ochronosis, alkaptonuria has been present, a condition in which homogentisic acid is present in the urine; this substance is formed from aromatic compounds such as tyrosine and phenylalanine, there apparently being in alkaptonurics an inability to break up the benzene ring in these substances. It would accordingly appear as if in some cases (a small proportion) of alkaptonuria, these aromatic compounds become oxidised into pigments(as is known to occur under the action of tyrosinase) and deposited in the tissues, producing the condition of ochronosis. In some cases ochronosis has followed the use of carbolic dressings for a long time, and the pigment is believed to be formed from the absorbed carbolic acid. This has been called *exogenous ochronosis.*

(2) **Hæmatogenous Pigmentation.** The pigments derived from the disintegration of hæmoglobin are of two main types, viz. those containing iron, and those without iron. In the normal hæmolysis constantly occurring, the latter are excreted chiefly by the liver as bile pigments, while the iron-containing moiety is retained mainly in an invisible form and the iron is used in blood formation. In pathological states hæmoglobin is broken up in closely similar manner and most cells seem to have the power to effect the change. The resulting

pigments may be deposited in the tissues around some *local destruction*, e.g. that following a hæmorrhage, or in certain organs when there has been a process of *general blood destruction*. When a hæmorrhage occurs into the tissues a certain proportion of the red corpuscles become hæmolysed, and their hæmoglobin is broken up by tissue enzymes. There thus arise various soluble pigments in different stages of oxidation, which produce the colours in the skin around a bruise. In many situations a considerable amount of effused blood may be absorbed without deposit of pigments, but in certain circumstances where absorption is imperfect, pigments are deposited in solid form. The formed pigments derived from red corpuscles or free hæmoglobin and deposited in the tissues are of two types, *viz. iron-free* and *iron-containing*.

(*a*) *Iron-free pigments.* The chief of these is known as *hæmatoidin*, which occurs in the form of characteristic rhombic crystals of mahogany brown colour, though also as needles and granules. Hæmatoidin is formed chiefly from somewhat large accumulations of blood ; thus the rhombic crystals are often met with in the sites of old cerebral hæmorrhages, in thrombi, hæmorrhagic infarcts, etc. It is found both in the free condition and within cells, but an extracellular formation has usually been assigned to it. While the possibility of this cannot be excluded, experiments by Janet Niven and myself show clearly that in certain conditions when red corpuscles are ingested by macrophages, formation of hæmatoidin crystals within these cells may follow (Figs. 99, 100). A similar intracellular formation of crystals may occur when the cells have ingested hæmoglobin in large amount.

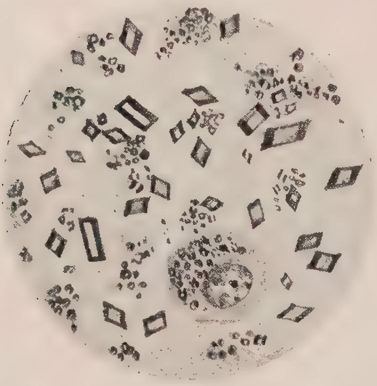


Fig. 98.—Hæmatoidin Crystals and Granular Pigment, some of the latter being within a Phagocyte. × 250.

Hæmatoidin has been found to have the same composition as bilirubin, and gives the same chemical reactions. In the van den Bergh reaction, we have now a delicate test for the presence of bilirubin, and its application has shown that, when blood is effused into the tissues or into cavities, there is soon formed a considerable amount of bilirubin which gives the indirect reaction (p. 631).

(*b*) *Iron-containing pigments.* When red corpuscles are ingested by phagocytes the hæmoglobin becomes broken up and a pigment is formed, at first diffuse, afterwards granular, which gives the chemical reactions of iron. The term *hæmosiderin* is applied to such pigment —it does not indicate a definite chemical substance, merely a pigment which gives the iron reaction. Hæmosiderin is usually seen in the form of yellow-brown granules, and is contained chiefly within cells. As in the normal condition, the reticulo-endothelial system plays in pathological states an active part in the metabolism of hæmoglobin, and deposits of hæmosiderin in it are of common occurrence. Within the phagocytic cells of the spleen or lymph glands, all stages of transition from incorporated red corpuscles to hæmosiderin may often be seen; and the pigment may present various depths of colour when treated with hydrochloric acid and potassium ferrocyanide, corresponding to stages of disintegration. Ultimately, the iron may be in a comparatively simple compound as is shown by its high percentage in certain conditions; for example, in the lymphatic glands in hæmochromatosis the amount of iron may be more than 10 per cent. of the dried substance.

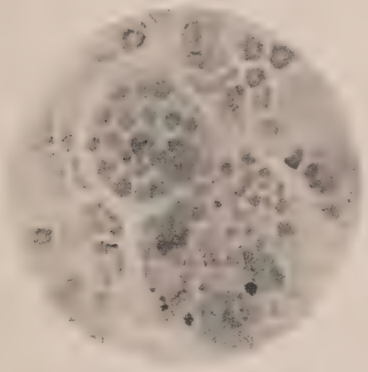


FIG. 99.—Two phagocytes from subcutaneous tissue of mouse containing numerous erythrocytes and some hæmosiderin granules, 6 days after injection of erythrocytes. × 750.

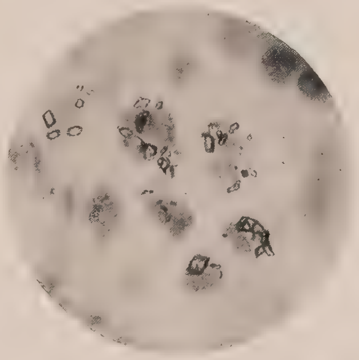


FIG. 100.—Intracellular formation of hæmatoidin in macrophages of mouse, 16 days after injections of hæmoglobin. × 600.

From preparations by Dr. Janet S. F. Niven.

We may add that when hæmoglobin in sufficient amount is introduced into the tissues it is absorbed by phagocytes, especially histiocytes, and the cytoplasm of these cells soon gives a diffuse iron reaction; thereafter granular hæmosiderin appears. Our experiments with Janet Niven referred to above also show that in such conditions crystals of hæmatoidin may form at a later date within the cells. It would appear also that in the case both of erythrocytes and hæmoglobin, the iron-reacting substance up to a certain stage may still contain the bilirubin moiety, and that this afterwards may be split off and crystallise as hæmatoidin.

The term 'hæmofuscin' has been applied by various writers to a pigment occurring in the form of minute brownish-yellow granules which do not give the iron reaction. Some consider that it may be formed from hæmosiderin, the iron becoming split off and disappearing; in this case the pigment is probably hæmatoidin or allied to it. Others again, e.g. Mallory, regard it as a preliminary product in the formation of hæmosiderin from hæmoglobin. From our own observations we have obtained no satisfactory evidence that a pigment which does not give the iron reaction, is formed in this way. Some of the iron-free pigment, e.g. that described as occurring in non-striped muscle, epithelial cells, etc., is of lipoidal nature—lipofuscin (p. 168) and its formation from hæmoglobin has not been established. Again, it is to be noted that hæmatoidin, which is iron-free, also is met with in the granular form. It is clear that the term ‘ hæmofuscin ’ has been applied to different substances, and it is very desirable that either it should be properly defined or its use discontinued.

When there is excessive *destruction of red corpuscles in the circulation*, as in certain infections and poisonings, the hæmoglobin is broken up in a way similar to that described. The iron-free pigment is excreted chiefly in the bile, which contains an excess of bilirubin, and to some extent in the urine and bile as urobilin. A certain increase of bilirubin may be detected in the blood, this giving van den Bergh’s indirect reaction (p. 631), though there may be no actual coloration of the skin. The process of blood destruction takes place in two ways. On the one hand, damaged red corpuscles are ingested by macrophages, Kupffer cells and other cells belonging to the *reticulo-endothelial system* (p. 82), especially in the pulp of the spleen ; and hæmosiderin is formed within them—a process of *hæmophagocytosis*. On the other hand, hæmoglobin may be set free in the plasma by *hæmolysis*, and be taken up by the cells of the kidneys (as well as by the reticulo-endothelial system), where hæmosiderin is formed and can be recognised by the usual tests. Hæmoglobin in solution is also passed in the glomerular filtrate into the tubules and is taken up by the cells of the convoluted tubules. If, however, the free hæmoglobin at any time exceeds a certain amount, it cannot be disposed of in this way ; it is then excreted in the urine, hæmoglobinuria resulting. This is well exemplified in paroxysmal hæmoglobinuria. The earliest iron reaction given by the kidney is a slight diffuse blue staining with ferrocyanide of potassium and hydrochloric acid. This may be found a few hours after hæmoglobin has been injected into the blood of an animal. A day or two later minute granules appear, and these then increase in size and amount ; ultimately the cells of the convoluted tubules may contain iron-reacting granules in large amount. When hæmolysis, with resulting hæmoglobinæmia, is continued for some time, hæmosiderin granules appear also in the liver cells. Experiments performed along with J. S. Young, however, failed to give us any evidence that hæmoglobin is excreted in the bile as had been stated by some writers to occur.

Accumulation of hæmosiderin in organs, or *visceral siderosis*, is met with in conditions of blood destruction, and can often be demonstrated at a post mortem examination by means of ferrocyanide of potassium and hydrochloric acid ; or by ammonium sulphide, which colours the hæmosiderin black. It is a marked feature in pernicious anæmia, the liver, and usually the kidneys and spleen, giving a strong reaction (Fig. 101); and it occurs in malignant malaria (*vide infra*). It is met with also where there has been much hæmorrhage into the tissues, e.g. in purpuric diseases. Moreover, in some severe infections, notably those due to hæmolytic streptococci, there may be a sufficient accumulation of iron to give a visible reaction. In paroxysmal hæmoglobinuria much hæmosiderin may accumulate in the kidneys, and a certain amount also in the spleen and liver. In the kidneys it is chiefly in the cells of the convoluted tubules. Our own observations show clearly that, when there is hæmoglobinæmia for some time even without hæmoglobinuria, the hæmoglobin is split up by the cells of the tubules of the kidney and the hæmosiderin is retained within them (Fig. 102). Thus the threshold value for the excretion of hæmoglobin depends upon the extent to which this change can be effected. When the hæmoglobin is in larger amount than can be dealt with in this way, then hæmoglobinuria occurs. Hæmosiderosis can be produced experimentally by various poisons such as toluylenediamine, pyrogallic acid, arseniuretted hydrogen, etc., and notably by a hæmolytic serum. Experiments which we carried out along with Shaw Dunn, showed that hæmosiderin, derived from blood destruction, when deposited in the liver and other organs, is rapidly used up again during the process of regeneration of the blood. In cases of visceral siderosis the relative amount of iron in the various organs (liver, spleen,

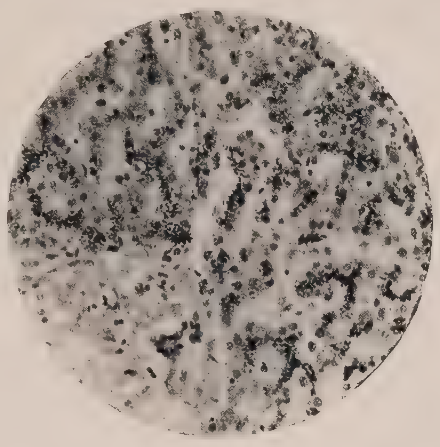


Fig. 101.—Granules of Hæmosiderin in Liver Cells, from a case of Pernicious Anæmia. × 250.

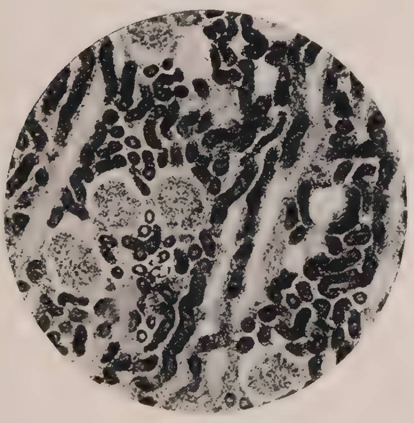


Fig. 102.—Rabbit's Kidney, showing extensive Deposit of Hæmosiderin in convoluted Tubules, the result of long-continued Hæmoglobinæmia without Hæmoglobinuria. × 60.

kidneys) varies greatly; this is notably the case in pernicious anæmia. This cannot be fully explained, but it would appear to depend in great part on the extent to which lysis and phagocytosis respectively are concerned in the process of blood destruction. The largest deposits of hæmosiderin, however, are met with in the disease known as hæmochromatosis (*vide infra*). We may add that hæmosiderin giving a distinct iron reaction is *normally* found in the liver and spleen of infants up to the third month of life.

Malarial Pigmentation. In malarial fever the parasites within the red corpuscles produce from the hæmoglobin a dark-brown pigment in the form of very minute granules, which accumulates within the intra-corpuscular parasites. It becomes free when the corpuscles are broken down, and is taken up by phagocytes and deposited in organs, especially the spleen and liver, where it remains practically unchanged for many years. Malarial pigment contains iron, though it reacts negatively with the ordinary Prussian blue test, and there is no evidence that it has any relation to melanin. W. H. Brown showed that in its solubilties and bleaching properties it differs from the latter and that a solution of it gives the spectroscopic bands of hæmatin. When there is much blood destruction, especially in severe cases of the malignant type, hæmosiderin may be deposited in the organs in addition to the malarial pigment.

Hæmochromatosis. This name was applied by v. Recklinghausen to a condition in which there is an extensive deposit of hæmosiderin in the organs and tissues, without anæmia or other evidence that there is increased blood destruction taking place. Along with the hæmosiderin there is sometimes a proportion of pigment which does not give the iron reaction; when present, it occurs chiefly in the non-striped muscle of the intestine. But the outstanding feature is the extensive deposit of hæmosiderin, which reaches a degree not met with in any other condition. Not only so, but it occurs more widely than that seen as the result of hæmolysis. The largest actual amount is present in the liver, but the hæmosiderin may occur in even greater concentration in the lymphatic glands in the upper part of the abdomen. It occurs in the skin, especially around the sweat glands, in the kidneys and spleen; also in the pancreas, gastric glands, heart muscle, sometimes in the thyroid, etc. In the liver it is always accompanied by a somewhat fine cirrhosis, usually with enlargement, and there seems to be no doubt that the cirrhosis precedes the deposit of pigment. In advanced cases, however, when the liver cells are stuffed with pigment granules, it is quite likely that they may become damaged and even undergo necrosis, and that in this way the cirrhosis may be intensified. There is often also cirrhosis of the pancreas, and, as a result of this, diabetes may be produced. This sets in usually at a somewhat advanced stage, at which there is often sufficient pigment in the skin to give a distinct brown colour—hence the term *bronzed diabetes.* Although bronzed diabetes is a rare condition, there is no doubt that hæmochromatosis in varying degree is a commoner condition than was formerly supposed. The etiology of hæmochromatosis is not understood. As has been said, there is no evidence of abnormal hæmolysis which would explain the hæmosiderosis, nor, in fact, is it certain that all the iron in the organs has been derived from hæmoglobin. There seems to be abnormal affinity of the tissues and organs for iron, and the large amount of iron which accumulates necessarily implies a retention of iron over a long period of time. It is not known, however, what leads to the retention of iron.

We may mention that, while in such a hæmolytic condition as pernicious anæmia the iron in the liver is about 0·3 per cent. of the dried substance, in hæmochromatosis it may reach 5 per cent. or more, while in the lymphatic glands it may exceed 10 per cent.

As we have said, the distribution of hæmosiderin in hæmochromatosis is of a striking character, occurring in organs such as the heart, stomach, etc., where deposits are not met with in hæmolytic states. Rous and Oliver have found, however, that when a rabbit is repeatedly transfused with red corpuscles over a period of several months, hæmosiderin accumulates in large amount and its distribution comes to correspond with that met with in hæmochromatosis. They think that in this disease the cirrhosis leads to failure of the liver to deal with the products of *normal* blood destruction, and hæmosiderin thus accumulates in the body and becomes deposited in widespread fashion. This may represent the sequence of events which occur, but we have no knowledge how such a defect in the liver is brought about or how it acts. Whether or not the iron in the tissues passes through the form of hæmoglobin before its deposit, it must ultimately come from the iron of the food. And calculations show that, with a generous estimate of the iron in the daily diet, the retention in the tissues of all the iron in the food for a period of years would be necessary to account for the excess present in some cases. At present, the grounds for a satisfactory explanation of the deposits of iron are wanting.

Mallory and his co-workers have shown that, by the administration of copper salts to rabbits over a considerable period, extreme pigmentation of the liver and cirrhosis result. The pigment, called by them ‘hæmofuscin,’ which accumulates in the rabbit's liver, does not give the iron reaction; (in the case of the monkey, however, they found that part of it did so). The hæmofuscin is supposed by them to be an intermediate stage in the formation of hæmosiderin, but no chemical data to support this are given. Mallory believes that hæmochromatosis in the human subject may result from copper poisoning, the sources of the copper being contaminated foods and distilled beverages. The subject has been investigated by other workers, but the results have been contradictory. At present it is not possible to say to what extent, if any, copper plays a part in the production of hæmochromatosis.

Biliary Pigmentation. This occurs especially in jaundice, the pathology of which will be considered in connection with diseases of the liver. At present we shall describe only the nature and distribution of the pigmentation. In the majority of cases of jaundice the coloration of the skin and other tissues is due to absorption of bile pigments from the liver, when the passage of bile is interfered with by some obstruction; the pigments are then in solution in the blood and lymph throughout the body; and in the adult, as a rule, there is no actual deposit except in the liver and kidneys when the condition has lasted for some time. As a result of the obstruction, the bile pigment retained in the liver cells becomes deposited in the form of small greenish-brown granules, these being usually most distinct in the central parts of the lobules. In the bile capillaries, the retained bile gradually becomes inspissated or thickened; ultimately elongated homogeneous casts of olive-green colour are formed within them, and not infrequently minute branches can be seen passing back from these into the interior of the liver cells. Such appearances are specially met with in obstructive jaundice of long duration. The bile pigment is excreted by the kidneys, and a finely granular deposit occurs in the cells of the convoluted tubules. Portions of the pigmented cells become broken off and form granular collections in the tubules, and these on passing downwards become condensed, so that in the lower parts hyaline cylinders of brownish-green colour may be present.

In children, however, for some reason which is not understood, bile pigment has a greater tendency to separate out in the tissues. Thus in the jaundice common after birth—*icterus neonatorum*—the bile pigment may become deposited in the form of minute needle-like crystals and rhombic prisms of hæmatoidin. This occurs notably in the kidneys, in the tissue between the tubules at the apices of the pyramids, and the term *bilirubin infarct* is applied.

(3) **Atrophic Pigmentation.** In the later years of life a fine brownish-yellow pigment tends to appear in the heart muscle, non-striped muscle, etc.; and in wasting diseases this accumulation of pigment tends to be more marked. In the heart muscle the pigment accumulates in the central part of the cells at the poles of the nucleus, and when this is associated with wasting of the muscle, the term *brown atrophy* is applied. Similar pigment may occur in the liver cells, especially in the central parts of the lobules, in the cells of the testis, and in the nerve cells of the cortex of the brain. In the last situation a considerable amount of pigment is met with in senile insanity and allied conditions, the change being known as *fuscous degeneration*. The pigment is to be distinguished from that which occurs normally in pigmented nuclei, e.g. in the locus cœruleus and substantia nigra, and which appears to belong to the melanin group. The exact nature of the pigment which occurs in brown atrophy, etc., is not known, but is believed to be chiefly of lipoidal nature, as it reduces perosmic acid to a certain extent, and is usually coloured by the sudan stains. It is often called *lipofuscin*.

(B) EXOGENOUS PIGMENTATION.

The most important variety of exogenous pigmentation is that produced by the entrance of dust particles through the respiratory passages. A certain amount of coal-dust and stone-dust enters and accumulates in the lungs of all individuals living in ordinary conditions, but the accumulation becomes excessive in the case of those whose occupation exposes them to an atmosphere rich in dust. The lungs may become infiltrated in this way by foreign particles of various kinds—coal, stone, iron, cinnabar and various organic substances—and pathological results may follow. These will be described later in connection with the diseases of the lungs, and at present we shall speak only of the distribution of the particles.

The entrance of such particles into the lungs is favoured by the presence of bronchial catarrh or other condition in which there is an interference with the action of the ciliated epithelium, but it is found that even in a quite healthy animal, dust rapidly gains access to the pulmonary alveoli if the amount in the inspired air be great. In a very short time the dust particles are taken up by phagocytes in the pulmonary alveoli and carried into the lymphatic system. The origin of the phagocytic cells has been a much disputed subject. They have generally been regarded as derived from the flattened alveolar epithelium, but recently certain observers claim that they are macrophages from the tissues. I consider that the former view is essentially correct, though the cells of epithelial origin may be afterwards added to by cells which have passed into the alveoli from the pulmonary stroma. Cappell has introduced carbon and other dust particles by intra-tracheal insufflation and has found that the particles are taken up by the alveolar epithelium before there is time for any emigration of macrophages from the tissues; and from the study of his preparations I can confirm his results. The particles ingested by phagocytes are then distributed throughout the connective tissue of the lungs, accumulating specially in certain sites, and results of irritation follow according to the nature of the particles. Large collections of carbon particles may be accompanied by little or no overgrowth of connective tissue, whereas this is very marked in the case of certain kinds of stone dust, the condition of silicosis resulting (p. 411). The particles are carried also to the bronchial glands, which become pigmented and enlarged; here also the changes will depend on the nature of the particles. The permanent accumulation occurs within the reticular and other cells. Occasionally in anthracosis, a lymphatic gland ruptures into a pulmonary vessel and pigment becomes distributed through the general circulation. It is then found especially in the spleen, where it may form small black areas visible to the naked eye, though also in the bone marrow and liver (Fig. 103). When accumulation of pigment has occurred in the lungs, there is a certain reversal of the process when an individual is removed to ordinary conditions, the pigment being carried into the alveoli by phagocytes and then removed in the sputum. This is seen, for example, in miners whose sputum has a black colour and contains much coal-dust —the so-called 'black spit.'

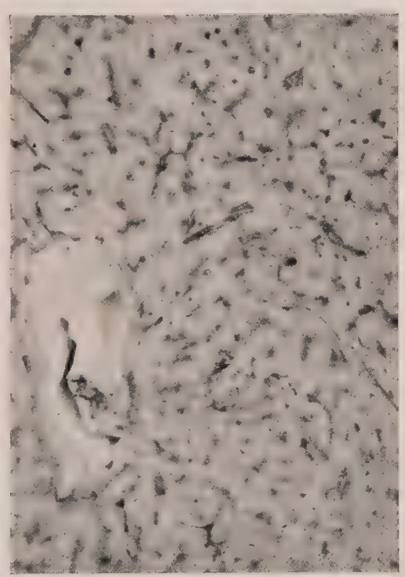


Fig. 103.—Anthracosis of liver showing deposit of carbon pigment especially in and around the portal tracts. (Dr. J. F. Heggie.) × 1½.

Examples of pigmentation due to absorption from the alimentary canal are of rare occurrence. The best example is *argyria*, which results from the taking of silver preparations for therapeutical purposes for a long period of time. Silver forms an albuminate which is carried to various parts of the body, and when it undergoes reduction many minute brownish-grey granules are formed. These are present especially in the wall of the intestine, in the skin, liver, and kidneys; and in the last mentioned they occur especially in the basement membrane of the collecting tubules, and to a less extent in the tissues around. The presence of the particles in the skin gives rise to a characteristic dusky appearance, which is of a practically permanent character. In the case of chronic lead-poisoning an albuminate is produced in a similar way, and the action of sulphuretted hydrogen on it round the teeth produces the well-known blue line on the gums.

In cases of tattooing, the fine particles such as Indian ink, ultramarine, cinnabar, etc., introduced through the skin, are taken up by histiocytes (p. 82) and lodge in small spaces or clefts in the connective tissue of the cutis. The particles are carried also by the lymph stream to the regional lymphatic glands and then are conveyed by phagocytes into the lymphoid tissue. Both at the site of introduction and in the lymphatic glands the pigment persists for an indefinite period of time.

CALCIFICATION

In this condition there occurs a deposit of lime salts, first of all in fibres or in matrix between the cells, or in dead or degenerating material. It differs from ossification inasmuch as the deposit occurs irregularly and without any definite relation to the organic matrix; it occurs also in excess, so that cretaceous material is formed, in which the cells of the part may be involved and killed. What may be regarded as almost a normal form of calcification is that seen in old age, especially in cartilage, e.g. the costal and tracheal cartilages. It has been supposed that it is due to the absorption of lime salts from the bones, which occurs in late life; but while this may play a part, probably the most important factor is some senile alteration in the matrix itself. In any case the process is closely related to that seen in pathological conditions.

Under normal conditions there is a constant flow of calcium from the small intestine where it is absorbed, to the kidneys and large intestine where it is excreted. Absorption and deposition also are going on in the spongiosa of bones. The calcium content of the blood is, however, kept at a comparatively constant level and various processes are concerned in maintaining the balance necessary. Such a balance clearly means control, and it has now been established that this is exerted by the parathyroid hormone. Hyperfunction of parathyroids leads to increased absorption from the bones and to hypercalcæmia, while hypofunction has the opposite effect. It is also now known that vitamin D plays an important part in influencing absorption of calcium from the bowel; a deficiency leads to diminished absorption and would lead also to hypocalcæmia were it not for the fact that the defect is made good, at least in great part, by bone calcium. Excess of vitamin D leads like parathyroid hyperfunction to hypercalcæmia and various secondary effects.

It must be understood, however, that the calcification in the tissues which occurs so commonly is due usually to *local changes* at the site of deposit, that is, independently of variations in blood calcium. There is, however, one notable exception—namely, that rare condition known as *metastatic calcification* which results from hypercalcæmia. The disturbances of calcium metabolism will be considered later in connection with the conditions of disease in which they occur. We shall first deal with the local deposits which are the result of affinity of the calcium in the blood and tissue fluids for certain degenerated elements.

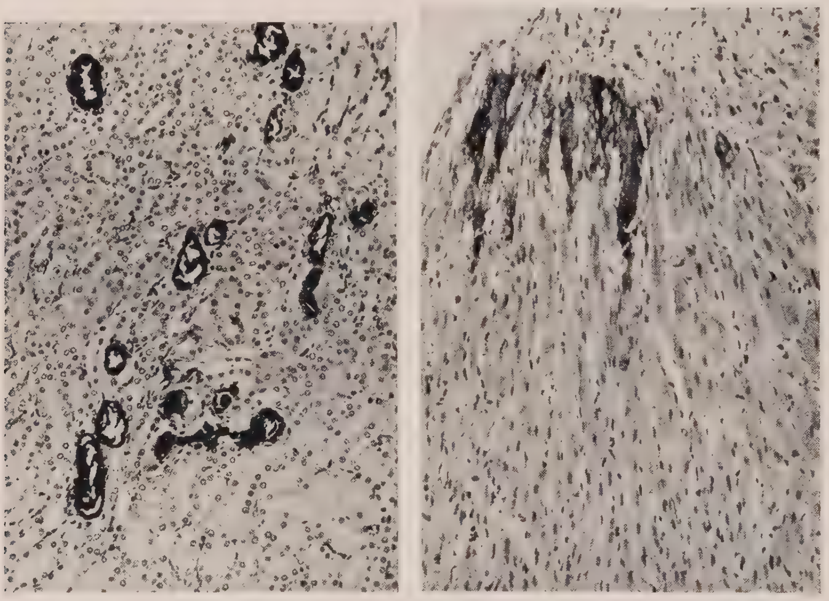
Conditions of Occurrence. It may be stated generally that dead tissue retained in the body tends to become impregnated with lime salts, and thus to assume a cretaceous character. Thus caseous tubercle, gummata, old infarctions, dead parasites, e.g. trichina spiralis and echinococcus cysts, also old collections of pus, degenerated material in atheromatous patches, etc., may become inspissated and calcified; in this way hard calcareous masses or plates may be formed. It is met with also in thrombi where there has been failure of organisation; in this way hard masses or ‘ phleboliths ’ are formed in veins. Closely allied to this is the calcification which occurs in dead cells or in collections of organic material and leads to concretions, e.g. in the vermiform appendix or in the duct of a salivary gland. It is to be noted that calcification occurs with special readiness in some kinds of animals, notably in rodents and herbivora which have a high blood calcium. For instance, if the cells of the kidney tubules of a rabbit be killed by any means, by artificial anæmia or by a poison, calcification soon follows in them; whilst the caseous lesions of tubercle in the bovine species become calcified at a very early stage. The affinity of fatty material for lime salts is strikingly illustrated in the case of fat necrosis, where the fatty acids set free by the pancreatic lipase combine with lime salts, and the dead patch becomes calcified (p. 134).

In many instances, however, there is neither death nor fatty change as a preceding condition, and the lime salts are deposited in tissue which shows a sort of hyaline condition. This is the case in the calcification of the media of arteries, and is of common occurrence in dense connective tissue, e.g. in the heart valves in chronic endocarditis, in the dura mater, in tendons, etc. In some cases again, it is impossible to say what is the antecedent change. Occasionally there occurs in some types of insanity and in the neighbourhood of gross lesions of the brain, an extensive calcification both of cerebral capillaries and of nerve cells, and it is difficult even to imagine what causes the deposit.

Calcification occurs also in tumours; it is common in uterine myomata undergoing involution after the menopause, and it is a striking feature in psammomata, where spherical masses form in concentrically arranged cells which have undergone a sort of hyaline change (p. 211).

It is noteworthy that calcification is sometimes followed by the formation of true bone in the affected area. This is of common occurrence in the calcified tuberculous lesions in children and is also occasionally met with in the calcified media of an artery.

Metastatic calcification is seen where there is abnormal absorption of lime salts from the bones; it is rare in the human subject. It has been observed especially in generalised osteitis fibrosa, also sometimes in osteomalacia; and the deposit occurs in situations which are otherwise rarely the seat of calcification, e.g. the wall of the stomach, kidneys, and lungs, as well as in the arteries, heart, etc. A similar metastatic calcification in arteries and various organs can be readily produced in animals as a result of hypercalcæmia brought about by excess either of parathyroid hormone or of vitamin D (Figs. 104, 105). In such conditions calculi often form in the bladder as the result of an excretion of calcium in excess by the kidneys.



Figs. 104 and 105.—Illustrations of hypervitaminosis D in rat.

Fig. 104, small calcified vessels in kidney; Fig. 105, calcified fibres of heart muscle—calcified parts appear dark,

From preparations kindly lent by Mr. J. R. M. Innes.

Lime salts have an affinity for hæmatoxylin, forming a lake with it, and the earliest sign of the change is given by the appearance of hyaline or finely granular material in the tissues, which is coloured a deep violet tint (Fig. 106). At a later stage the lime salts form irregular and somewhat refractile masses. The lime salts are of course readily soluble in weak acids, and small bubbles of carbonic dioxide are given off from the carbonates. When weak sulphuric acid is used as a solvent, the characteristic crystals of calcium sulphate separate out; this occurs more readily when the sections are in 50 per cent. spirit, in which the crystals are little soluble. When lime salts are treated with nitrate of silver, yellow phosphate of silver is formed, and this quickly undergoes reduction on exposure to light and gives a black colour.

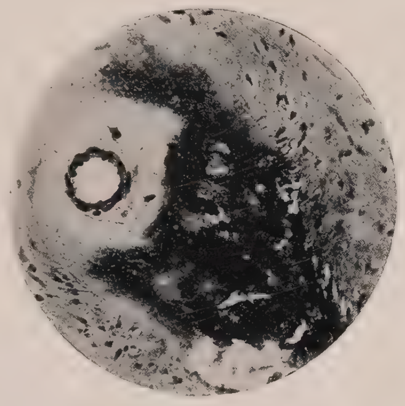


FIG. 106.—Area of Calcification near a Blood Vessel in a Tumour (Fibroma).

The dark colour is the result of staining with hæmatoxylin, and the earliest change, in the form of fine granular deposit, is seen at the margin. × 200.

Both the hæmatoxylin and silver nitrate tests are of use in showing calcium deposits, but they are not specific. Cameron has shown that silver nitrate is reduced by other substances, e.g. iron, and that the reaction with hæmatoxylin is given by a substance formed before the deposit of lime; the latter reaction is given after the tissue is decalcified. He finds that the best reagent is alizarine, the staining principle in madder, or its derivatives. Alizarine stains calcium salts a red colour, but the reaction may not be given by very old deposits. When injected *intra vitam* it colours growing bone (but not fully formed bone), also deposits of lime salts unless they are very old.

It may be noted that in many instances calcification is associated with deposit of iron compounds which give a Prussian blue reaction. These may give a diffuse staining or may be in granular form.

Pathology of Calcification. The salts deposited correspond to those in ordinary ossification; they are chiefly calcium salts, with a small admixture of magnesium salts. It has been found that the proportion of phosphates and carbonates is about the same as in bone, nearly nine times as much calcium being in the form of phosphate as of carbonate. With regard to the conditions determining the deposit we have to consider the blood and lymph, on the one hand, and the state of the tissues at the particular site, on the other. Theoretically any excess of lime salts in the blood, diminished amount of carbonic dioxide or increased alkalescence, will aid deposition. The first of these factors leads to the metastatic calcification already mentioned; and the sites of deposit can be explained in part on the basis of loss of acid with increased local alkalescence. Hence the deposit occurs in the stomach around the glands which secrete hydrochloric acid, and also in the kidneys, whose cells excrete acid. The relative rarity of calcification in the veins, as compared with the arteries, has been supposed to be due to the carbonic dioxide in the venous blood; the more frequent occurrence of degenerative lesions in the arteries is probably, however, the important factor.

Apart from cases of metastatic calcification, however, it cannot be said that any disturbance in calcium metabolism plays an important part in *local calcification*. The absorption of lime salts from the bones which occurs in old age has been supposed to lead to senile calcification, but it seems much more likely that the chief factor is constituted by the changes in the connective tissues such as hyaline and fatty degeneration. It may be noted in this connection that in tissues prone to calcification there may occur an increase of calcium without visible change as age advances; calcium is thus ready at hand for deposit. This is seen in the case of the aorta (Andrewes). In cases of local calcification we have accordingly to look mainly to changes in the tissues themselves for the explanation of the occurrence.

The special tendency for collections of dead and degenerated material to become calcified, has long been recognised, and this has been explained as due to a chemical affinity of fatty material for lime. Klotz came to the conclusion that there first occurs a splitting of the fat, and that the fatty acid combines with calcium to form a soap. The fatty acid then becomes replaced by phosphoric and carbonic acid, and the ordinary deposits of lime result. A striking instance of such combination of lime with fatty acids is seen in the case of fat necrosis. But in a great many instances there is no evidence of preceding fatty change, and where it does occur, it is still doubtful whether a calcium soap ordinarily forms a stage. In dense fibrous tissue, in elastic tissue, and in smooth muscle fibres, a hyaline stage precedes the deposit, and it has been supposed that the deposit represents a physical rather than an ordinary chemical process. Wells takes this view, and in support of it he found that, when various dead tissues were introduced into the peritoneal cavity of the rabbit, and examined after a time, hyaline cartilage took up by a process of adsorption more lime salts than did any other tissue. These results suggest, although the subject is still obscure, that it is on such principles that the process of calcification in tissues which are not the seat of fatty change, depends. Certainly the microscopic appearances suggest a similarity in these cases to the senile calcification of cartilage. In the experimentally produced metastatic calcification following hypercalcæmia above referred to, the lime may be deposited in tissues apparently healthy.

URATIC INFILTRATION

Deposit of urates in the tissues of the joints and in other parts is a well-marked feature of *gout*. The deposit consists mainly of biurate of sodium, and occurs chiefly in the cartilage of joints—the metatarso-phalangeal joint of the big toe, the knee-joint, and joints of fingers, being those most frequently affected. The superficial part of the cartilage is specially affected, and it presents a dull whitish appearance, as if covered with white paint. Urates are deposited also in the soft tissues of the joints, in the eyelids, in the cartilages of the ear, and in the subcutaneous tissue, especially of the hands. They may form nodules of considerable size, called *tophi*, and the skin over them may ulcerate, and hard chalk-like masses become discharged. Microscopic examination shows that the urates are in the form of bundles or sheaves of closely-packed needle-crystals (Fig. 107), and when abundant have a brownish colour. In the soft tissues there is evidence of slight irritation around them, and foreign-body giant-cells may be present (p. 87). The large masses may be attended with a certain amount of necrosis of the infiltrated tissue. In the joint cartilages the deposit occurs first in and around the cells, unlike what is seen in calcification, and according to some observers it is preceded by degenerative changes in the cells. In the kidneys deposits of urates are not uncommon in the tubules at the apices of the pyramids, where they give rise to a pale streaking. They occur also in the tissues around, where they may cause a certain amount of necrotic change which may be attended by formation of foreign-body giant-cells. Such deposits are met with, however, in fibrotic kidneys apart from any manifestations of gout.

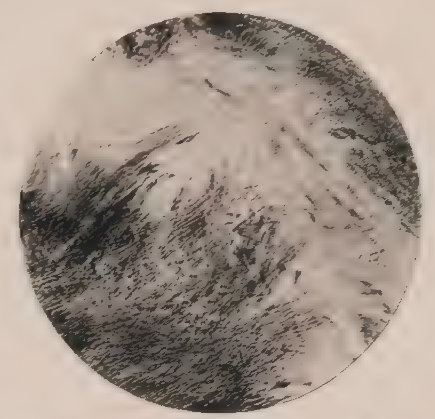


FIG. 107.—Section through Gouty Nodule of Skin, showing Deposit of Needle-like Crystals of Biurate of Sodium. × 250.

Whilst the tissue changes in gout are of a characteristic nature, little is known of the nature of the underlying error of metabolism or its cause. The deposits described may occur without much pain or discomfort, but on the other hand, the patient may suffer from attacks of acute gout, during which the joint and the tissues around become intensely painful and inflamed, as if there were some diffusible irritant present. Some authorities consider that such attacks are due to increased deposit of urates taking place; others ascribe them to the absorption of urates from the deposits and their diffusion in the tissues around. The amount of uric acid in the blood is, as a rule, distinctly increased, without corresponding increase in other nitrogenous products of metabolism; this increase of uric acid is more marked in those who suffer from the acute manifestations of gout. It is to be noted, however, that a similar condition of the blood may exist in some cases of nephritis, without evidence of gout; and in leukæmia even higher amounts of uric acid in the blood may be met with. For a short time before an acute attack of gout there is usually a diminished excretion of uric acid in the urine, while during the attack and for some days afterwards, the amount is increased. In those suffering from gout, fibrosis of the kidneys, arterio-sclerosis and high blood pressure often develop, and in this way a fatal result may be brought about. It is worthy of note that chronic lead-poisoning often leads to a form of gout with corresponding vascular changes.

In children, shortly after birth, there are commonly found deposits of uric acid and urate of ammonium in the collecting tubules of the kidneys, so that the medulla shows brownish-yellow streaking. Such collections, which are called *uric acid infarcts*, have usually no pathological significance, as they soon disappear. Sometimes, however, they persist, and minute concretions may originate in connection with them and pass into the pelvis, where they may grow and form renal calculi.

Glycogenic Infiltration. The deposit of glycogen within cells occurs in various pathological conditions, but interpretation of its significance is not clear, and it cannot be said to be of great importance in relation to disturbance of carbohydrate metabolism in general. In diabetes, owing to the conversion of glycogen into sugar, there is a marked diminution in the amount of glycogen in the liver and muscles, the chief seats of normal deposit, while the amount in the heart muscle is usually increased, and a deposit occurs in the kidneys, especially in Henle's tubules. The latter deposit probably results from a re-absorption of sugar, but the cause of the increase in the heart muscle is not known. There occurs in this disease an increase of glycogen in the polymorpho-nuclear leucocytes, in which cells a small amount may be detected by the microscope in normal conditions. In these cells a marked increase occurs also in various inflammatory states; in fact, as a rule, where there is a distinct leucocytosis. Leucocytes which have emigrated from the vessels may similarly contain glycogen, also those in recently formed pus, though the glycogen soon disappears. It is doubtful what such accumulation of glycogen in leucocytes represents. In certain tumours, e.g. chondromata, epitheliomata, and especially in the so-called hypernephromata, glycogen may be abundant, but here also it is not possible to give the explanation. Glycogen is more abundant in embryonic than in adult tissues, and accordingly one might expect it to be more abundant in actively growing tissues, but its distribution in tumours is related rather to the nature of the tissue composing them than to their activity of growth. In view of the fact that glycogen is sometimes found along with fat, e.g. at the periphery of necrotic areas, it has been suggested that its presence depends upon an interference with oxidation, but such an explanation can have only a limited application.

As glycogen is soluble in water, tissues to be examined for its presence must be fixed in alcohol. The glycogen occurs in minute granules or droplets, and is stained reddish-brown with iodine, and crimson in Best's carmine method, this latter giving very clear pictures. After death, glycogen rapidly becomes changed into glucose and is then not recognisable by microscopic methods

Glycogen Storage Disease. This disease which occurs in infants and children was first described by von Gierke. Two main types have been found. In the one the liver alone or the liver and kidneys are greatly enlarged as the result of an abnormal accumulation of glycogen in the liver cells and in the cells of the tubules of the kidney. In the other type the heart is chiefly affected and its weight may be several times the normal, the enlargement being due to a similar accumulation of glycogen within the muscle cells. The affected cells are swollen and appear vacuolated, the vacuoles containing glycogen which is more resistant to post mortem hydrolysis than normally. Other tissues besides those in which enlargement is obvious are also affected, *e.g.* skeletal and to a less extent visceral muscle, lymphoid tissue and even the brain. Thus the glycogen is stored chiefly but not exclusively in the enlarged organs. There is increase of the glycogen in the blood, most of it being within cells; the blood sugar in the fasting state is low. Acetone bodies are often present in the urine. These changes are accompanied by marked retardation in growth. The lesions apparently represent a defect in the metabolism and mobilisation of carbohydrates by the affected tissues but the real nature of the abnormality is not known, nor is the reason for the variations in the distribution of the stored glycogen understood.

CHAPTER V

INFECTION, IMMUNITY, FEVER

INFECTION

Infection may be said to occur when the tissues are invaded by living organisms and pathological changes are produced. Actual invasion is essential, and we may take as the criterion of this the penetration of organisms into parts normally free from them; and the general statement may be made that such penetration is always accompanied by some morbid change, though it may be slight. The invasion of organisms usually takes place into the interstitial tissues, as in tuberculosis, pyogenic infections, etc., but sometimes into a tube or space lined by a mucous membrane, which is normally bacterium-free, e.g. the gall-bladder or urinary passages. Symptoms of disease and even death may be in a few instances produced by absorption of toxins without actual infection, in the sense defined; for example, the absorption of the toxins of the B. botulinus from the intestine. The tetanus bacillus also has little or no power of invading the tissues; it flourishes in lesions produced by other organisms or in dead tissue, and the symptoms of tetanus are due to toxic absorption. In pathology we have to deal with the action of the organisms within the body, but it is essential in connection with etiology that the sources of the organisms and the paths of infection should be recognised. We shall consider this subject in the first place.

Paths of Infection. In the great majority of cases, the infecting organisms reach the body either by (*a*) direct contact, or (*b*) by the inspired air, or (*c*) by ingested food or drink. They then effect an entrance through the skin or mucous membranes. This statement applies to nearly all the bacterial infections, to many diseases produced by filter-passing organisms, and to many infections caused by metazoal parasites. In a smaller but very important group, the organisms are introduced into the body by the bite of an animal, usually an insect; in this case the method is really one of direct inoculation and the conditions differ somewhat from those of the first group. Transmission of disease by insects is common in the case of protozoal infections, e.g. malaria and sleeping sickness, and spirochætal infections, e.g. relapsing fever. It occurs also in infections with filter-passing organisms, e.g. yellow fever, dengue, etc., and is met with even in metazoal infections, e.g. filarial disease. It is exceptional in bacterial diseases, but the transmission of plague by fleas is an outstanding example. In certain infective fevers, the exact mode of infection is still unknown. The conditions of infection in the former group, where the organisms themselves effect an entrance into the tissues, may first be considered.

We have, in the first place, the very important fact that the tissues and fluids in the interior of the body are normally in a practically sterile condition; though occasionally organisms may gain access to the blood without causing disease, as they are quickly destroyed. We have another important fact, namely, that the skin and the mucous membranes of the alimentary tract and upper respiratory passages, harbour bacteria of various kinds, and that many of these have pathogenic properties. Every individual thus carries with him possible sources of infection. It has further been established that the organisms of various specific diseases, e.g. diphtheria, cerebro-spinal fever, cholera, etc., may be added to the ordinary bacterial flora of mucous membranes, and may flourish without any harm resulting. Individuals in whom these organisms are present are called 'carriers' in relation to the particular organism—'meningococcus carriers,' 'diphtheria carriers,' etc. The 'carrier' condition may result also when an individual passes through an attack of a particular disease, the organisms persisting on mucous surfaces after the acute infection; this is the common origin of the condition in the case of typhoid, the gall-bladder being the usual site of growth of the bacillus. Such individuals, although harbouring the pathogenic organisms, may not be, according to our definition, infected by them; though they may be the means of leading to infection in others. Often, however, the carrier is the subject of chronic infection with the organism in question and shows a definite lesion. The organisms may be passed on from one individual to another until, under favourable circumstances, the particular disease is produced. It is thus seen (*a*) that potential causes of disease are *normally* present, and (*b*) that the causal agents of specific diseases are *occasionally* present on mucous surfaces, and we have to consider the circumstances which bring about infection.

Conditions aiding Infection. It may be said that any condition which lowers either the *local* or the *general* resistance favours infection. Thus conditions like fatigue, cold, disturbed metabolism, act in this way. In specific fevers a lowering of the general resistance is an important feature and secondary infections are thus of common occurrence; this is especially noteworthy in influenza. It is well established too that normal individuals in health vary in susceptibility, so that under given conditions some become infected, while others escape; that is, diminished resistance or susceptibility may occur naturally in addition to being acquired. The virulence of organisms, that is, their power of invading and damaging the tissues, also varies greatly. This is known from the results of experimental inoculation of animals with different strains, as well as from what occurs during epidemics. In one epidemic, for example, a large number of people are infected or the disease is severe ; whilst in another the converse is the case. In addition to lowered general resistance and special virulence of organisms, the presence of *local lesions*, sometimes of a minute character, may play a very important part in leading to infection. This is clearly seen in the case of ‘ poisoned wounds ’ of the skin, where a slight scratch or abrasion may become infected, and no doubt the same holds in the case of mucous membranes. Injury to a bone predisposes to tuberculosis or to pyogenic infection, as will afterwards be considered, and many other examples might be given.

The question may, however, be put—can organisms invade a healthy mucous membrane or skin surface ? For all practical purposes an affirmative answer may be given, although, of course, it is impossible to say that any part is absolutely healthy. The entrance of the meningococcus occurs through the naso-pharynx, but in many cases of cerebro-spinal fever no abnormality can be detected in the mucous membrane, and a similar statement applies to the ‘ carrier ’ condition. As has been said above, the diphtheria bacillus may multiply on an apparently normal mucous membrane, and it can hardly be doubted that it may damage the epithelium by its toxic action and thus lead to a true local infection. Accordingly while local lesions play an important part in leading to infection, it must be admitted that virulent organisms may cause infection through a healthy mucous membrane. A similar statement probably applies to infection through the skin ; the anthrax bacillus and virulent pyogenic organisms may gain entrance through hair follicles and then invade the tissues. Further, it has been shown in recent years that deficiency in certain elements of food, notably vitamin deficiency, increases general susceptibility. This is seen in patients suffering under natural conditions from the effects of vitamin A deficiency and also to a striking degree when animals have been artificially deprived of this accessory factor. There results a remarkable effect also on mucous membranes, the epithelium being changed more to a squamous type, whilst numerous inflammatory affections may be set up by the bacteria normally present, these greatly increasing in number (p. 124). In scorbutic conditions too, due to deficiency of vitamin C, the proneness to inflammatory lesions from secondary infection is a prominent feature (p. 487).

In the case of diseases transmitted by *insects*, the mode of infection is sufficiently clear, but it does not follow that the mere introduction of the organisms into the tissues will lead to the disease. In fact, experimental work shows clearly that they may be killed off without harm resulting. Here also, just as in the first group, virulence of the organisms and the susceptibility of the individual are important factors in determining whether disease will or will not follow.

Distribution of Organisms in Infections. In order to understand the effects of organisms in producing disease and the mode in which different parts of the body are infected, it is essential to know the distribution of organisms after infection has occurred, that is, after they have gained a foothold in the tissues. In the first place, it may be stated that there may or may not be a *primary lesion* at the point of entrance. By this we mean a lesion caused by the invading organism, not a lesion predisposing to infection ; the latter has been discussed above. In the majority of bacterial infections such a local lesion is present, and is often a prominent feature ; this is well seen, for example, in typhoid fever, diphtheria, erysipelas, pneumonia, etc. But whilst such is the rule, there are instances where the site of entrance cannot be traced. For instance, in primary tuberculous infection of the alimentary canal in children, an ulcer is sometimes present, but on the other hand, frequently nothing can be found ; although a lesion may be too small to be discovered or one may have healed. In cases of severe staphylococcus and streptococcus infections also, it may not be possible to find any primary lesion to indicate the path of entrance. In the case of protozoal infections produced by the bites of insects, e.g. malarial infection, there occurs the usual reaction produced by the toxic secretion of the insect, but there is no characteristic lesion caused by the parasite itself.

With regard to the lesion at the site of infection, when such occurs, it may be said to be usually of *inflammatory* nature. It may be acute and may show special features according to the nature of the organisms, as already detailed, or it may be of more chronic nature as in tuberculosis and syphilis. It is unnecessary to give details here, as descriptions of such lesions will be found in subsequent chapters. Inflammatory reaction tends to restrict the organisms and often leads to their destruction, and the inflammatory changes then gradually pass off. The organisms may, however, pass the leucocytic barrier and be carried to the lymphatic glands, where they may be destroyed, or, on the other hand, may produce serious lesions. In the case of the pyogenic organisms, inflammation and suppuration may result, whilst in tuberculosis there may be the formation of tubercle nodules, caseation, etc. Even in normal conditions, as has been said, organisms may enter the blood stream from time to time, and of course when local infection has occurred, this is more likely to happen.

Another point of importance in relation to the clinical aspects of disease is that when a local lesion has healed and symptoms of infection have disappeared, the organisms may not be completely killed off but may persist in a quiescent state. At a later period, as the result of trauma or other cause, they may again become active and give rise to new lesions at the original site or in other parts. A focus of infection supposed to be healed may accordingly be the means of causing what may appear to be a fresh infection. Such an occurrence is met with, for example, in pyogenic infections both of the soft parts and the bones, and it is specially common in tuberculosis.

Septicæmia and Pyæmia. When bacteria gain a foothold and multiply in the blood, the term *septicæmia* is applied, and as this is a condition of great importance it must be further considered. In certain acute bacterial infections in the lower animals, for example anthrax in the guinea-pig, the organisms rapidly invade the blood stream from the site of inoculation and may be found on microscopic examination of the blood. In the human subject, however, it may be said that in septicæmia organisms are rarely so numerous as to be detectable on microscopic examination of the peripheral blood, though they may be often readily obtained by culture from it. It may be noted that they are more abundant in the capillaries of the internal organs than in the peripheral circulation, as is shown by microscopic examination of the tissues after death. In one type of case, where there is an absence of resistance to the organisms, the latter actively multiply in the circulating blood and as a rule a fatal result soon follows. This is seen in some cases of virulent streptococcus infection, and it is well exemplified in meningococcus septicæmia, where death may follow with remarkable rapidity without the occurrence of meningitis. In another type of case the organisms in the blood represent an overflow from the tissues into the blood stream, and here their significance is not so grave. To such a condition the term *bacteriæmia* is usually applied. The outstanding examples of this are the typhoid and paratyphoid infections, in which organisms can usually be cultivated from the blood at an early period of the disease. In the course of the infection, even before the healing of the lesions, the organisms disappear from the blood. So also in acute pneumonia, pneumococci may be obtained from the blood, and these disappear at the time of the crisis. Accordingly, the presence of organisms even in considerable number in the blood, does not necessarily mean that they will increase progressively. In bacterial endocarditis of the less acute type, organisms may be shed into the blood during a long period of time, as is shown by making cultures from the blood, and there is little doubt that if the source of supply could be removed, the normal sterile condition of the blood would soon be restored. In certain infections, however, active proliferation of the causal organisms in the blood is the characteristic feature apart from any special gravity of the condition, e.g. relapsing fever and malaria.

It will readily be understood, however, that when bacteria gain entrance to the blood in any way, there is always the risk that they may settle in some part of the body and produce serious lesions; ‘the complications,’ as they are called, of many diseases are brought about in this manner. Sometimes the secondary lesions are of the form of multiple abscesses, and then the condition is termed *pyæmia*. These pyæmic abscesses may be produced in two ways. On the one hand, the organisms circulating in the blood may settle in the capillary walls of various organs, where they grow and produce minute abscesses. This is typically exemplified in some cases of staphylococcus infection, e.g. in acute suppurative osteomyelitis; and certain organs are specially prone to be the seat of these abscesses, notably the lungs, kidneys, and heart wall. On the other hand, the organisms may be disseminated by portions of infected thrombi, which become mechanically arrested, and suppurating infarctions are the result. In this way, abscesses may be produced in the lungs in cases of septic thrombosis of veins, and in various organs in cases of bacterial endocarditis.

It is thus seen that after infection has occurred, the organisms may remain localised; they may be carried by the blood stream and produce corresponding inflammatory lesions in other parts of the body; or they may multiply in the blood stream and cause a true septicæmia.

Production of Toxins. In infection there is, however, another important factor in addition to the multiplication of the organisms and their distribution in the body, namely, the production of poisons or toxins. It may be said that all the important effects are the result of toxic action, and these effects are manifested on the one hand by tissue changes, and on the other hand by symptoms.

The toxins produced locally lead to the phenomena of inflammation around the organisms, and the characters of the inflammatory reaction are regulated by the nature of the organisms and also by their virulence. Thus while pyogenic bacteria usually cause marked leucocytic reaction, organisms of extreme virulence produce mainly damage to the vessels with accompanying inflammatory œdema, and often comparatively little leucocyte emigration in response; and there is evidence that certain organisms produce toxins which have an inhibitory effect on the leucocytes. Locally, of course, toxins may be comparatively concentrated and so the inflammatory changes may be explained. But in addition, toxins are absorbed from the site of bacterial growth and are carried by the blood stream throughout the body. Hence there is often seen in infections a general toxic action, the injury being more diffuse but less severe. Various retrogressive changes are thus produced in various organs—cloudy swelling, fatty degeneration, sometimes foci of actual necrosis. These are most marked in highly specialised cells and in organs concerned in the excretion of toxins, especially the kidneys and liver. General damage to the capillary walls may lead to the occurrence of minute hæmorrhages or petechiæ, and some of the eruptions in exanthemata are thus produced, although in some the organisms are actually present, e.g. in typhoid. In certain chronic infections, notably in tuberculosis and syphilis, amyloid change may result from the long-continued toxic action on the capillary walls.

Of the *symptoms* produced in infections the most important is fever, which will afterwards be considered more in detail. The effects of toxins are exerted also in the case of the nervous system, and varying degrees of disturbance of the mental faculties and of consciousness are met with up to complete coma. In some instances, the bacterial toxin has a specific effect on the nervous system ; for example, tetanus toxin leads to hyperexcitability of reflexes and tonic contraction of muscles. In the case of the toxin produced by the *Bacillus botulinus*, the action is mainly on the nuclei of the cranial nerves, and leads to symptoms of paralysis.

It is beyond the scope of this work to consider the *nature* of bacterial toxins, but a few facts of importance in relation to the pathology of infection may be given. In some instances the bacteria, when growing in a fluid medium, give rise to toxins which can be separated by filtration through porcelain or other filters. Such toxins are often spoken of as *extracellular toxins* or *exotoxins*. They have often characteristic effects as poisons, and, as a rule, they lead to antitoxin formation when injected in suitable doses into an animal. Diphtheria toxin, tetanus toxin, botulinus toxin, and some others belong to this group ; they are probably proteins, but nothing is known of their constitution, and they can be recognised only by the effects which they produce when introduced into the tissues. In the case of a number of organisms, however, especially many of those which invade the tissues and give rise to inflammatory and suppurative changes, no characteristic exotoxins can be obtained. Toxic phenomena may result when the dead organisms are injected, and there is no doubt that the bacterial protoplasm contains poisonous substances which become free on the disintegration of the bacteria. The term *intracellular toxins* or *endotoxins* has therefore been applied to such poisonous constituents of bacteria.

It is to be noted that endotoxins derived from different bacteria have pretty much the same action when injected into the body, and that there is usually a want of the specific effects which are found in the case of exotoxins. In relation to this, however, it must be borne in mind that in most infections occurring naturally, the symptoms of poisoning are not of characteristic nature. Fever with its associated phenomena is common to the majority, and the special features in any particular disease are due to the distribution of the organisms and the parts affected, rather than to the production of specific toxins. The community of action of endotoxins of different bacteria is accordingly quite in harmony with clinical facts. There is, however, evidence that organisms growing in the tissue fluids may produce toxins which are not formed in culture media ; to such toxins the term *aggressins* has been applied. We are justified in ascribing the tissue changes and symptoms of diseases to bacterial or other toxins, but it is to be recognised that the nature and mode of action of the poisonous substances are in many instances imperfectly understood. Also the factors which cause predilection of particular organisms for special tissues are mainly unknown.

In addition to the various phenomena described—invasion by micro-organisms, their further distribution in the body and the production of toxins—processes of reaction go on during an infection, as is shown by the appearance of antibodies in the blood. Thus both cure and a condition of immunity result.

IMMUNITY[1]

When an animal is insusceptible to infection by a given organism, it is said to possess immunity against it, and the term is similarily used in relation to the action of toxins. In the case of all organisms and all toxins some animals are found to be susceptible, others to be immune; and the latter are said to possess a *natural immunity* against the organism or toxin respectively. Variations as regards immunity and susceptibility are met with naturally also amongst individuals of the same species, and this fact explains in part the incidence of disease amongst individuals equally exposed, notably in epidemics. It will also be readily understood that there are all degrees of such natural immunity, or, in inverse ratio, of natural susceptibility. In an animal or person naturally susceptible, immunity may become developed, and it is then called *acquired immunity*. The fundamental fact with regard to this type of immunity, established by clinical observation a long time ago, is that the passing through an attack of infective disease in many cases confers immunity, sometimes practically for the rest of life. Manifestly some profound changes are produced in the body by such an attack of the disease, and we have to consider the nature of these. We do not intend to deal in detail, however, with the methods of producing immunity, and shall give merely the main facts established which bear on the nature of the reaction in the body.

Active Immunity. The earliest methods of producing immunity artificially rest on the fact just mentioned as a basis, and consist in producing a mild attack of the disease, or, to speak more generally, in introducing into the body the causal organism in such a weakened or attenuated form that no serious harm results. In all such cases the immunity which develops is called *active immunity*, as it is due to a *reaction* of the tissues of the person or animal treated. Thus in Jenner's method of vaccination against smallpox, the individual is inoculated with the virus of the disease attenuated (in relation to the human subject) by its growth in the tissues of the bovine species. Such a virus is capable of producing infection in the human subject, but this is of a slight and passing kind. The methods of Pasteur in vaccinating against such diseases as fowl-cholera, anthrax, and hydrophobia, depend on the same principle—the introduction of a weakened virus, this being afterwards followed by inoculation with one more virulent. The next important advance came with the discovery of the fact that the presence of *living* organisms was not always necessary for the production of immunity. Thus on the one hand, it was found that active immunity against an organism may be produced by injection of the particular organisms in the dead condition; and on the other hand, that immunity against a toxin can be developed by the injection of graduated doses of the particular toxin. The latter fact, first established in relation to tetanus and diphtheria toxins, was found to hold also in the case of other toxins produced by plants and animals, e.g. ricin and abrin, snake and other venoms. Nevertheless, there are of course many potent poisons, including alkaloids, neutral principles, etc., towards which immunity cannot be produced in this way, and it is likely, as will be explained more fully below, that for the production of immunity, it is necessary that the poison should be of protein constitution. The term *vaccines* is usually applied to organisms, in the living or dead condition, injected for the purpose of developing immunity.

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[1] For further details consult *A System of Bacteriology*, Medical Research Council, Vol. VI. London, 1931. Bordet, J., *Traité de l' immunité*, Paris, 1939.

The next important fact is that the substances which lead to immunity on injection have the remarkable property of giving rise to *antibodies*, the presence of which is detectable in the blood serum by methods to be presently explained. The term *antigen* is now ordinarily applied to any substance or body which gives rise to an antibody, and it may be said that antigens include also a great number of proteins which are in no way concerned with the production of disease and have no toxic properties. There is also evidence that certain lipoid and polysaccharide constituents of organisms may act as antigens. In order that antigens should give rise to antibodies, it is essential as a rule that they should enter the tissues and blood in an unchanged condition, which means by some other route than the alimentary canal, that is parenterally.

Another all-important fact is that the relationship between the antigen and its antibody is, within limits, of a specific character, that is, an antigen gives rise to the formation of an antibody which reacts only with the antigen which has led to its development. This last statement, however, needs the qualification that reaction may occur with an antigen of closely similar character; for example, an antibody to one bacterium may have a certain action on a closely allied bacterium, but this action is probably due to there being a certain number of antigenic molecules common to the two organisms. There are also some other exceptions to the general law of specificity, but these need not be considered. The almost specific nature of antibodies is, however, one of their most characteristic features, and the number of antibodies would appear to be practically limitless.

Passive Immunity. We have explained that the term 'active immunity' is applied when the state of immunity is the result of a reaction on the part of the tissues of the individual or animal concerned. Immunity, however, can be conferred on an individual by the injection of the serum of an animal highly immunised against the particular organism or toxin. In this case the term 'passive immunity' is applied, as the tissues of the individual thus becoming immune take no part in the process. Hence it is a transferred immunity, and depends on the antibodies present in the serum of the actively immunised animal. Passive immunity is conferred at once on the injection of the antiserum, whereas active immunity is relatively slowly developed ; on the other hand, passive immunity is of relatively short duration, usually of not more than two or three weeks. Passive immunity may be efficient against either a toxin or a living organism, that is, may be antitoxic or antibacterial, according to the nature of the antigen employed in producing the antiserum. We shall now give an account of the varieties of antibodies which may appear in the blood of an actively immunised animal, and on the transference of which the production of passive immunity depends.

Antibodies. Practically nothing is known as to the essential nature of antibodies, though they have been found to be associated especially with the globulin fraction of the serum and may be provisionally regarded as representing proteins specifically modified. Their recognition as antibodies depends entirely on certain biochemical or bio-physical reactions, and therefore they may be conveniently classified according to these reactions. On this basis, we may speak of the following, namely (*a*) *antitoxins*, (*b*) *agglutinins*, (*c*) *precipitins*, (*d*) *immune-bodies* and *lysins*, (*e*) *opsonins*. It must not be inferred, however, that these represent *distinct* classes of substances. Agglutinins are closely allied to precipitins and the latter again to the immune-bodies which fix complement. We may state, however, that an antiserum is composed of overlapping moieties each of which can be recognised by a particular effect. With this explanation we may now consider their chief characters.

(*a*) *Antitoxins.* As has been said, immunity may be developed against many toxins, and this is associated with the appearance of antitoxins in the blood serum. By properly graduated doses of the toxin injected, as is carried out in the preparation, for example, of diphtheria antitoxin, the amount of antitoxin in the serum may ultimately reach a high level. So far as is known, the antitoxin has no other effect on the toxin than that of neutralising it by combining with it. Ehrlich's view was that the toxin molecule is to be regarded as possessing two groups which play different parts in the phenomena of poisoning. By one of these, called by him the *haptophore* group, the toxin becomes anchored to cells of the body, and then the other, the *toxophore*, exerts its harmful effects. Antitoxin, by combining with the haptophore group, prevents the combination of the toxin with the tissue cells. It apparently does not materially alter the constitution of the toxin or destroy it ; in fact, in certain instances the toxin can be separated again from its union with antitoxin.

Ehrlich's view with regard to the dual constitution of toxins is supported by the fact that they may undergo change to form what are known as *toxoids*. These are toxins which have lost their toxicity in varying degree but still can combine with antitoxins in virtue of their haptophore group. They thus act as antigens and can be used as such in the process of active immunisation. Toxoids may form naturally from toxins in course of time or they may be readily produced from them by treatment with various chemicals such as formalin, iodine, etc.

(*b*) *Agglutinins.* In this case, the antibody unites with the antigen (the bacteria or other organisms) and causes clumping or agglutination of the organisms previously distributed as a uniform suspension in saline fluid. Here again there is a specific union of the two bodies, antigen and antibody, and the agglutination results from some physical change specifically produced, which appears closely allied to precipitation (*vide infra*). It may be added that the presence of electrolytes is necessary for the occurrence of agglutination. Whether or not agglutination *per se* is of importance in connection with immunity, so far as the destruction of organisms in the body is concerned, the development of agglutinins is part of the immunity reaction, and proceeds on the same lines as that of other antibodies. In view of what has been said in regard to the specific nature of antibodies, it will be seen that agglutination can be used for purposes of diagnosis, and that in two directions. In a case of disease, agglutination of the particular bacterium (under proper precautions) by the serum of the patient, in sufficient dilution, points to infection with that bacterium ; the disease may thus be diagnosed. On the other hand, a particular antiserum can be used to identify bacteria ; for instance, if in the case of a particular bacterium the agglutination titre of the serum corresponds with that in the case of the bacterium used as antigen, the two bacteria may be regarded as of the same species. Agglutination may thus be used for the identification of organisms as well as for the diagnosis of diseases.

(*c*) *Precipitins.* As has been mentioned, the formation of antibodies is not peculiar to the case of organisms and their products, but occurs also with numerous harmless proteins, provided that they are foreign to the tissues of the animal injected. The serum of an animal injected into another animal of different species is followed by the appearance of an antibody which is called a 'precipitin,' because it leads to the formation of a precipitate when added to the serum used for injection. Each precipitin thus produced may be regarded as practically specific, that is, it produces its action only with the serum used for injection ; though there is also sometimes to be observed a slight reaction with the sera of allied species. Precipitins can be prepared by the injection of an endless variety of protein substances, and though they by their precipitating effect do not play any important part in immunity to disease, their development corresponds with that of other antibodies. The precipitin reaction has been extensively used in medico-legal work for distinguishing human blood from that of other animals.

(*d*) *Immune-bodies.* Sometimes when bacteria of a particular species are injected into the body, the serum comes to have the power of killing and dissolving them. It is then said to have *bactericidal* and *bacteriolytic* properties. In some cases the normal serum possesses such properties, and these become greatly increased in the process of immunisation. This lytic action can be acquired also against other formed elements ; for example, when the red corpuscles of an animal are injected into another animal of different species, the serum of the latter acquires the power of dissolving the corpuscles used for injection. This acquired lytic property of the serum depends in each case on the development of an antibody which is called an *immune-body* or *sensitiser*. This immune-body, however, does not of itself produce the lysis, but requires the co-operation of a labile substance normally present in the serum, which is called *complement* or *alexin*. Thus when a hæmolytic serum is heated for an hour at 55° C. it loses its hæmolytic property, but this can be restored by the addition of normal serum, which contains the complement. The immune-body, which is an antibody with specific properties, as explained above, unites with the red corpuscles and makes them sensitive to the action of complement, and it is accordingly often called a ‘ sensitiser.’ Red corpuscles treated with the corresponding immune-body are spoken of as ‘ sensitised corpuscles ’ and can be used for testing for the presence of complement ; if complement is present they will undergo lysis, if absent they will remain unchanged. It may be added that complement does not increase in amount during the process of immunisation. In the process of lysis the complement is used up or fixed.

We see then that acquired bacteriolysis or hæmolysis depends on a variety of antibody—immune-body or sensitiser—but this requires complement in order that the characteristic effect may be produced. Sometimes, however, an immune-body is developed without there being any corresponding lytic property, and the presence of the immune-body can then be shown by the fact that the antiserum along with the corresponding antigen, leads to the fixation or absorption of complement, as in the case of lysis ; the fixation of complement is shown by the fact that when sensitised corpuscles are added to the mixture after a suitable interval they do not undergo lysis. Thus we may define an immune-body more generally, as an antibody which, in combination with its corresponding antigen, leads to the *fixation of complement*. Complement fixation can thus be used for diagnosis in the same way as agglutination ; neither will occur unless both the antigen and the corresponding antibody are present together.

An illustrative example of complement fixation may be given as follows. (The term 55° C. means that the serum has been heated for an hour at 55° C. to destroy the complement.) Two tubes, (*a*) and (*b*), are prepared with the following contents :—(*a*) Antigen + antiserum 55° C. + complement ; incubation for an hour. Sensitised corpuscles then added remain unaffected ; fixation of complement has occurred in the first stage. (*b*) Antigen + normal serum 55° C. + complement ; incubation as before. Sensitised corpuscles then added undergo lysis because there has been no fixation of complement during the period of incubation.

(*e*) *Opsonins.* In connection with the subject of inflammation, we have stated that normal serum contains a substance called opsonin which leads to the phagocytosis of bacteria. This substance is labile like complement and is destroyed at 55° C. In the course of immunisation, however, against a bacterium an antibody is developed which has the character of a *specific* opsonin, and thus the serum acquires greatly increased properties against the particular bacterium used for injection, but not against other bacteria. The normal complement-opsonin, however, does not increase in immunisation. The specific opsonin developed in immunisation has the relative heat-stability and other properties of antibodies in general. The opsonic antibody may exert its action in two ways. It may act without complement and is then known as a *bacteriotropin*, and it may, like an immune-body, lead to the union of complement in increased amount, the action of the latter being thereby intensified—it may then be called an *opsonic immune-body.* The all-important fact is that in immunisation against bacteria, opsonic antibodies are developed which lead to a more effective phagocytosis of the organisms concerned. Metchnikoff showed that the phenomena of phagocytosis are closely related to immunity. In an animal naturally immune against an organism, active phagocytosis occurs when the organism is introduced into the tissues. On the other hand, in a very susceptible animal, there is little or no phagocytosis ; the organisms flourish freely and may sometimes lead to septicæmia. He further showed that when an artificial immunity is produced, this condition is associated with an active phagocytosis and the destruction of the organisms ; and he supposed at that time, that some change had occurred in the leucocytes as the result of immunising the animal. It is, however, now known that these phenomena depend upon the increase of the opsonic properties of the serum and not on any essential change in the phagocytes.

The mechanism of opsonic action. Emigration of leucocytes and their subsequent movement in the tissues, as we have said, is to be ascribed to chemotaxis (p. 69). These and other cells may move towards organisms and afterwards ingest them, but this is not the explanation of phagocytosis resulting from the action of opsonins.

The phenomenon both *in vitro* and *in vivo* is far too rapid to be produced in this way. In an *in vitro* experiment, for example, numerous cocci may be ingested under the influence of normal serum in a minute or two. Two factors are concerned in the process. On the one hand, opsonins produce physical changes in the bacteria, amongst which are alterations in surface tension and adhesiveness. On the other hand, a force allied to agglutination draws the bacteria around the leucocytes. The bacteria thus brought into contact with leucocytes adhere to them and are then engulfed in their protoplasm. The whole process may thus occur apart from amœboid movement on the part of the leucocytes. In certain cases, however, contact with micro-organisms is effected by the leucocytes actively moving towards them.

The development of antibodies which act as opsonins is without doubt of the highest importance in immunity. It leads to increased phagocytosis or to the occurrence of phagocytosis where otherwise it would be absent, and there is ample evidence that intracellular digestion is of the highest importance in the destruction of organisms. In some instances bacteria appear to flourish well within the leucocytes and other phagocytes, but in most cases their ingestion by the cells is followed by their dissolution.

The appearance of antibodies in the blood, which is one of the most important phenomena of immunity, is to be regarded as in some way the result of altered cellular activity. After immunity has been actively produced, the antibodies in the blood gradually diminish in amount, but they may be recognisable for a considerable time. When they have disappeared, a certain degree of immunity may still be present, and we must suppose that some change in the cells is left—probably the change which is the basis of the production of antibodies. And this change may be demonstrated by the more rapid way in which antibodies are produced when the antigen originally used is again introduced into the tissues. We may add that a ‘ tissue immunity,’ for example of the skin, may be obtained against streptococci, the anthrax bacillus, etc., which does not depend on antibodies in the blood. Sometimes it is due to a local accumulation of phagocytes.

The above facts with regard to immunity have been established chiefly in the case of bacterial diseases, but all the main principles apply also to *virus diseases.* Active immunity can readily be produced by modified viruses ; in fact, smallpox was the first disease against which it was obtained. The active immunity thus produced varies greatly in duration. In many diseases such as smallpox, varicella, measles and yellow fever, it is practically life-long, but in some diseases, e.g. foot-and-mouth disease and the common cold, it soon passes off. Also, the presence of antibodies is shown in many instances by the fact that a passive immunity can be produced ; this can be effected in some instances by the transference of a comparatively small amount of immune serum, e.g. in measles and yellow fever. The application of *in vitro* methods for demonstrating the presence of antibodies is of necessity restricted, but it has been carried out in various cases. For example, the complement-fixation test can be applied in foot-and-mouth disease, while a flocculation reaction is got in smallpox by interaction between the serum of the patient and an extract from the skin lesions. In short, immunity in bacterial and in virus diseases would appear to correspond in all essential points.

SUPERSENSITIVENESS AND ANAPHYLAXIS

Various substances when introduced into the body of certain individuals, produce definite symptoms of greater or less intensity, whilst they are relatively or completely innocuous to normal individuals. The term *supersensitiveness* is applied in a general way to such a condition of abnormal susceptibility, and there are a number of varieties of this state. For example, some people are specially affected by the ingestion of certain articles of diet, such as strawberries, shell-fish, etc., urticaria and other symptoms resulting. The sensitiveness possessed by various people to the pollen of grasses, resulting in hay fever, is another striking example. In some cases supersensitiveness is clearly acquired, in others it is apparently natural ; though in instances of the latter the possibility of its being acquired cannot always be excluded. This will be more fully explained below. But if the whole group of such phenomena is considered, we may say that in some cases the supersensitive state may be developed in a manner corresponding to that in which immunity is produced, that is, by the *development of antibodies* in response to the introduction of proteins which act as antigens. To this variety of supersensitiveness the term *anaphylaxis* is applied. On the other hand, in another group of cases there is no evidence that an immunity reaction is concerned though supersensitiveness appears. The term anaphylaxis means a state opposite in nature to immunity or protection ; but it must be noted that it applies to the *result* of the process, not to the nature of the reaction by which it is produced. In any given instance of supersensitiveness, there arises the definite question whether, in view of what is known with regard to anaphylaxis, it represents an antibody reaction or not.

Phenomena of Anaphylaxis. The condition of anaphylaxis may be produced by the injection of a great many varieties of foreign proteins which are harmless to normal animals, and it is to be noted that the anaphylactic symptoms are pretty much the same in a given species of animal, no matter what protein has been used for injection. For instance, if a small amount, 0·01 c.c. or even less, of horse serum, be injected into a guinea-pig, the state of anaphylaxis is established in about ten days. The animal is then said to have become anaphylactic or *sensitised*, and if a small quantity of horse serum be injected, preferably intravenously, severe symptoms occur almost at once. The animal staggers and falls over, convulsive movements and signs of embarrassment of respiration appear, and death may rapidly follow. The fatal result is brought about mainly by asphyxia due to a spasm of the muscular walls of the bronchioles, the lungs passing into a condition of acute over-distension. We have thus the essential fact that symptoms of acute poisoning, with a fatal result, are produced in an anaphylactic or sensitised animal by the injection of a substance which is harmless towards a normal animal. The development of anaphylaxis in other species of animals rests on a similar basis, but the anaphylactic symptoms vary in character, and are brought about in various ways. Thus in the rabbit, death is mainly due to contraction of the pulmonary arterioles, whilst in the dog there occurs a remarkable accumulation of the blood in the liver and portal system, with shock-like fall of the blood pressure.

As we have already said, a close analogy exists between immunity and anaphylaxis, so far as the development of the two conditions is concerned. Both are produced by the parenteral introduction of foreign proteins, which act as antigens and anaphylactogens respectively. In both there is a period of incubation ; and both possess the features of specificity as explained above. Further, if the blood serum of an anaphylactic animal is transferred to a normal animal, the latter becomes anaphylactic, though often this does not occur at once but some time afterwards. In other words, there is a *passive anaphylaxis* corresponding with passive immunity, and it may be added that in each case the passive type lasts a shorter time than the active.

It is admitted by every one that the symptoms of anaphylaxis depend in some way on the combination of antigen (anaphylactogen) and the corresponding antibody, but it is still uncertain how the particular effects of poisoning are brought about. According to one view, a poison is produced in the circulating blood,—the so-called *humoral theory*. But there are serious objections to this view. Many points are still obscure, but the bulk of evidence seems to show that the chief phenomena of anaphylaxis are due in some way to the interaction of antigen and antibody within the cells, rather than to a poison formed in the circulating blood. Such a hypothesis, known as the *cellular theory*, is supported by various facts. It has been found that the separated tissues of an anaphylactic animal are supersensitive to the action of the antigen. For instance, Dale, by using the isolated uterine muscle of the guinea-pig, showed that the muscle of a sensitised (anaphylactic) animal was stimulated to contraction in quite a different way from that of a normal animal. When the specific antigen was applied, the muscle underwent a sudden contraction which passed off after a few minutes ; thereafter the muscle was desensitised. This result was obtained after the blood had been washed out of the muscles as far as possible by perfusion with Ringer's solution. Lewis considers that this disturbance in the cells may lead to the setting free of a histamine-like H-substance, which in its turn may cause certain of the vascular changes and œdema associated with the anaphylactic state. The possibility that some of the symptoms of anaphylaxis are due to the formation of toxic bodies in the blood cannot, however, be as yet entirely excluded. Further, a fall in complement is a noteworthy feature of anaphylactic shock and the nature of this fall is still unknown.

Anaphylaxis in the Human Subject. In the human subject anaphylaxis may develop as the result of injection of foreign (heterologous) serum ; for example horse serum, as in the prophylactic injection of antitetanus serum. In some cases, severe symptoms have occurred when, after the necessary interval, a second dose of serum has been injected, especially by the venous route ; and in one or two instances a fatal result has followed. Evidence of the existence of the anaphylactic state may be obtained by injecting into the skin a small quantity of serum, when there results a local area of inflammatory œdema, not seen in a normal individual. But the danger of anaphylaxis may be avoided to a considerable extent if the serum be injected gradually in small amounts.

Another example of anaphylaxis in the human subject is seen in the so-called *serum disease* which has been met with when horse serum, usually in the form of antidiphtheritic serum, has been injected subcutaneously. This affection is characterised by the occurrence of inflammatory œdema at the site of injection, and sometimes by a corresponding swelling of the related lymphatic glands ; other symptoms are slight pyrexia, urticaria, pains in joints, leucopenia, etc. Such phenomena may be met with eight days or longer after a single injection of the serum, or when a second injection is given after an interval of about twelve days or more. In the latter case, the symptoms appear shortly after the second injection—the so-called immediate reaction. The occurrence of the immediate reaction is readily intelligible according to the view that the person has been sensitised or rendered somewhat anaphylactic by the previous injection. The symptoms appearing after a *single* injection are probably capable of explanation on the same basis. It may be supposed that in the latter case, when the antibodies appear in the blood after an injection, there is still a certain amount of antigen present, and that the combination of these two may lead to the phenomena described. The symptoms recorded are met with in only a small proportion of cases where serum is injected. They are usually not of severe nature and soon pass off. The evidence available seems to us to indicate that the serum disease depends on an anaphylactic reaction, though some writers hold that it is not justifiable to take such a view.

Supersensitiveness in Infections, Allergy. The supersensitiveness to bacterial products developed in the course of an infection, is a subject of high importance and one which has wide bearings. The existence of such a condition was first established in the case of tuberculosis by Koch, who showed that individuals suffering from this disease were more sensitive to the action of the products of the tubercle bacillus than were normal individuals; and a similar condition was afterwards found to hold in other infections. The supersensitive state may be evidenced by special *local* reactions, inflammatory swelling, etc., at the site of injection, by corresponding *focal* reactions round the lesions, and by a *general* reaction, in particular by the occurrence of pyrexia. Such reactions are now made use of for diagnostic purposes, in the tuberculin and mallein tests for tuberculosis and glanders, especially in veterinary practice. Local reactions are seen sometimes not only when the bacterial products or dead bacteria are actually injected, but also when they are applied to a surface epithelium, such as that of the conjunctival sac, as in Calmette's tuberculin reaction. Apart from the subject of diagnosis, the facts known with regard to this form of supersensitiveness are of high importance in connection with the general pathology of infection. For they show that in many instances an individual becomes during the infection more sensitive to the products of the invading organisms than he was before. In other words, owing to the acquired susceptibility, the bacterial products formed and absorbed come to exert an increasingly disturbing effect on the tissues and metabolism. The same principle has been applied to other conditions. For example, it is possible that the active manifestations of rheumatism are due to an increased activity of the organism (possibly a streptococcus), its products then acting on tissues already rendered supersensitive by pre-existing infection. It has already been suggested that the phenomena seen in acute nephritis may be due to the toxins, probably of streptococci, acting on the capillaries of the glomeruli and body generally which have been sensitised in a similar way, the chief result of the action being an abnormal permeability. To what extent such views will be substantiated remains to be determined, but there can be no doubt that the altered sensitiveness produced by infections is a fact and it must play an important part both in the tissue changes and in the symptomatology of disease. The term *allergy* (altered reactivity) is now usually applied to this type of supersensitiveness.

Idiosyncrasies, Atopia. It has long been known that some persons possess a special sensitiveness to certain substances. These may be introduced (*a*) by inhalation, as in asthma and hay fever, (*b*) by alimentation, as in the case of certain articles of diet, e.g. strawberries, shell-fish, milk, eggs, etc., or (*c*) by contact, as in the case of primulas and other plants. Many of the symptoms such as bronchospasm, nasal and conjunctival irritation, œdema, skin eruptions, etc., correspond to those of anaphylaxis. Idiosyncrasies run in families and are frequently of hereditary nature. In many instances, notably in asthma and hay fever, supersensitiveness can be shown by introducing the particular substance intradermally. A connection between anaphylaxis and idiosyncrasy, on the one hand, and immunity, on the other, appears from the fact that the former conditions, like the latter, can be transferred to a normal individual. On injecting intradermally a minute quantity of the serum of the supersensitive patient and then, after an interval of some time has elapsed, the particular substance concerned, an inflammatory reaction results at the site. To idiosyncrasies of this kind the term *atopia* has been applied. The transference of the condition depends on the presence of an antibody usually known now as a *reagin*, in the blood of the supersensitive individual. Reagins have, however, not been shown to possess any of the other properties of antibodies which have been described above.

In the case of supersensitiveness to articles of diet, it is possible that, owing to a special peculiarity of the individual, protein molecules or their derivatives may pass through the intestinal mucosa in a state so little changed that they may function as antigens and give rise to antibodies. That the development of antibodies may be produced in this way is shown by the fact that Ehrlich was able to immunise animals against ricin and abrin respectively by feeding them with these vegetable poisons. Supersensitiveness to drugs may in certain cases have a similar basis, compounds being formed with tissue constituents which excite a reaction leading to supersensitiveness.

FEVER

Elevation of the temperature above the normal occurs in a variety of conditions—infections of various kinds, lesions of the nervous system, heat-stroke—and can also be produced experimentally by certain drugs. It is advisable, however, to apply the term 'fever,' as is now usually done, to that condition of disordered metabolism associated with pyrexia, which occurs in many infections. But at the same time we do not exclude the possibility that a similar condition may be produced by other causes.

In an attack of fever, three stages are generally recognised, viz. (*a*) the *onset*, (*b*) the period when the fever is established, often called the *fastigium*, and (*c*) the stage of *defervescence*, during which the temperature falls to normal. During the *onset* the patient feels cold and shivers, and sometimes a rigor is present; at the same time the internal temperature is rising and may reach a considerable height. The blood vessels of the skin are contracted, as are also its non-striped muscle, so that a condition of goose-skin is often present. The state of the skin causes lowered surface temperature, hence the sensation of cold, and there is diminished loss of heat. The involuntary contraction of the muscles in shivering and rigor contributes to the increased metabolism and increased production of heat. During the *fastigium* the vessels of the skin become dilated, the face becomes flushed, and there is general feeling of heat and discomfort. Usually the secretion of sweat is interfered with, and the skin is dry, though a considerable amount of moisture is still being lost by insensible perspiration. Sometimes, however, notably in rheumatic fever, there is much perspiration. The temperature, which is elevated to a varying extent, may show only slight diurnal variation as in pneumonia, or distinct morning fall as in typhoid, or again it may have an irregular course. The occurrence of *defervescence* with fall in the temperature may be comparatively rapid, by *crisis*, as is well seen in acute pneumonia, and this is accompanied often by perspiration and increased loss of heat; or, on the other hand, defervescence may occur gradually, by *lysis*, the fall extending over several days, as in typhoid. It may be added that after the temperature falls to normal the increased discharge of nitrogen, which is one of the features of fever, may be continued for a day or two. This has been observed in acute pneumonia, where it has been ascribed to the absorption of proteins present in the exudate.

The increased temperature in fever is manifestly the result of a disturbance of the factors which in health lead to the balance of heat production and heat loss. It is unnecessary to enter in detail into the mechanism of the normal control. It is sufficient to keep in view the main facts, namely, that the loss of heat is due to the physical processes of conduction, radiation, and evaporation of moisture, and that these depend mainly on the distribution of the blood and the secretion of sweat, as controlled by the nervous system. Increased production, apart from muscular work, on the other hand, is a matter of chemical regulation, the metabolism responding, in a way which is not fully understood, to increased requirements. During the *onset*, when the patient feels cold, there is distinct interference with the loss of heat, and this in itself might cause rise of temperature, but in addition, increased production of heat has been found to be present at this stage; there is thus a combination of diminished loss and increased production of heat. During the *fastigium* it has been found that the temperature of the skin is raised; there is thus increased loss by radiation and conduction. The dryness of the skin appears to be mainly the result of more rapid evaporation, as it has been found that the loss of moisture by the skin may not be actually diminished. Of course, with a given surface temperature the heat loss is still greater when the sweat glands are acting in excess, as is sometimes the case. This increased loss of heat maintained for a time implies, of course, increased production, and the latter has been clearly established by studies in metabolism in fever. There is increase in the respiratory exchange, with other evidence of excessive metabolism, and it has been found that the amount of heat lost during fever in a given time may be more than 50 per cent. above the normal, though usually it is less than this figure. This increase has been found especially in acute fevers such as typhoid, malaria, etc., but the increase in others may be comparatively slight.

As a rule then, during the course of the fever, heat production and heat loss are increased in approximately the same degree, whilst the temperature is maintained at an abnormally high level. While increased heat production is thus an important factor in fever, it cannot be taken as in itself the explanation of the pyrexia. For example, in a normal individual much more heat may be produced by muscular exercise than ever occurs in fever, and this may take place without a rise in the internal temperature corresponding with what is seen in febrile pyrexia. Furthermore, in exophthalmic goitre and other forms of hyperthyroidism, the basal metabolism, which means the number of calories lost in a given time by an individual at rest in bed and in the fasting condition, may be 60 per cent. or more above the normal. It is accordingly clear that in addition to increased heat production in fever, there is a fault in the *temperature-regulating mechanism*, so that the loss of heat necessary to adjust the temperature within normal limits does not occur. Liebermeister expressed this by saying that in fever the heat regulation is adjusted to a higher level or *norma* than in health. This might be due, however, to a fault in control, or failure to keep the temperature down in the conditions present; and of course there is no definite level in fever analogous to a normal temperature. It is to be noted that a fall of temperature may be artificially produced in fever, e.g. by cold baths, or by antipyretics, to an extent which does not occur with a normal temperature; this is another indication that the temperature-regulating mechanism is less efficient than in health. Accordingly, two factors emerge for further consideration, namely (*a*) over-production of heat and (*b*) interference with the regulation of the internal temperature. It is advisable, however, to consider first some points in the metabolism.

Metabolism in Fever. It has long been recognised that excessive metabolism of protein is one of the most important features of fever. There is a great increase in the excretion of nitrogen in the urine in the form of urea, ammonia and other nitrogenous bodies; the proportions of these vary in different cases, although the two last are often relatively increased. Independent observations have shown that in typhoid fever the excess of nitrogen excretion may sometimes represent a loss of four or five pounds of muscle in a week. There is an increase also in the excretion of sulphur and phosphorus for the same reason. Marked interference with the digestive and absorptive mechanisms is, of course, present, and an ordinary fever diet is usually not sufficient to supply the necessary calories for a normal individual, much less so for a fevered patient. The carbohydrates in liver and muscle are soon used up; there is not sufficient absorption of these substances to take their place, and thus a certain degree of inanition or starvation is ordinarily present. The body has accordingly to live on its proteins and fats; the respiratory quotient usually falls in consequence and general wasting occurs. Apparently owing to the deficiency of carbohydrates necessary for the efficient oxidation of fats (*vide* p. 946), acetone bodies not infrequently appear in the urine. Urobilin in considerable amount may be present in the urine, and apparently results from the increased blood destruction which occurs, and which may lead to a varying degree of anæmia.

The true nature and significance of the increased protein metabolism in fever are still matters of dispute. Most of the changes mentioned correspond with those met with in inanition, and are in part to be ascribed to this cause, as a fevered patient is in a condition of partial starvation and has to subsist in part on his proteins. But this factor is quite insufficient to explain the amount of protein metabolism in fever ; and in a starving individual there is no increased production of heat such as occurs in the latter condition, the basal metabolism on the contrary being diminished. Artificial elevation of the temperature in starving dogs has been found to raise the metabolism of proteins, and a similar result has been obtained in the human subject by raising the temperature by means of hot baths ; such increase in protein metabolism is, however, relatively slight.

These two factors, inanition and elevation of temperature, are in themselves insufficient to account for the febrile metabolism, and accordingly other explanations have been looked for. One view is that the increased metabolism is the result of direct action of bacterial and other toxins on the proteins of the body, especially those of muscle. It is known that toxins such as are acting in fever have a harmful effect on protein, as indicated by cloudy swelling, etc., and it is thus possible that a general action of slighter degree may result in increased metabolism, although no visible structural change may be present. In support of this view, it has been generally stated that it is not possible to prevent the protein disintegration by means of other food constituents, especially carbohydrates ; and various observations have given negative results. Shaffer and Coleman found, however, that by the use of diets of high caloric value, containing protein with a large proportion of carbohydrate, it was possible to diminish greatly, or even prevent, excessive protein metabolism in typhoid fever. Furthermore, and this is a point of much importance, they considered, from the diminished excretion of creatin and sulphur, that the katabolism of tissue protein was really diminished. If this is the case, the diets in question apparently acted by saving proteins necessary for the production of heat, as it does not seem possible that they could prevent increased metabolism brought about by direct toxic action. Some authorities accordingly believe that the metabolic changes of fever represent chiefly those necessary to maintain the increased temperature and, to a less extent, those resulting from inanition.

Another view is that the increased temperature in fever represents simply a reactive process with beneficial effect ; we have already seen that it is *not necessarily* the result of increased heat production (though this is present), as in normal individuals the rise of temperature would be prevented by increased loss of heat. Some years ago the view was put forward that the increased temperature had a prejudicial effect on the invading organisms, but for this there has been found no satisfactory evidence. The results of more recent work, however, show that the heightened temperature may have a favouring effect in the defence of the body by stimulating the production of antibodies. There are clinical facts in agreement with such a view, as the non-occurrence of the ordinary pyrexia in a fever, for example pneumonia, is often an unfavourable sign, and comparisons might be drawn between fever and a known reactive phenomenon like leucocytosis. It has been found also that the injection into an animal of a certain dose of bacterial products may give rise to pyrexia, whilst a large dose may be followed by fall in temperature and collapse. Such considerations are, however, not conclusive. If the reactive nature of pyrexia were established, a new light would be thrown on the significance of fever, but the question would still remain as to whether all the metabolic changes could be interpreted simply as those necessary for keeping the temperature at a level above the normal.

THE SYMPTOMS of fever are to be regarded as the combined result of the increased temperature in itself and of the action of toxins produced by the infecting organisms ; and the effects of both of these factors become accentuated by continued duration of the pyrexia. Rise of temperature caused by exposure to hot moist atmosphere leads to marked increase of the pulse-rate, tendency to dyspnœa, general discomfort, headache, etc. It was shown by Halliburton and Mott that a temperature of about 108° F. continued for some time, causes coagulation of the globulin in the nerve cells, but no doubt finer molecular change is brought about at a lower level. And in this connection it may be noted that patients who have recovered from heat-stroke may suffer from nervous symptoms for a considerable period afterwards. It can hardly be doubted, however, that toxic action is the more important factor. It is a matter of common clinical experience, for example, that the effects on the functions of the body and especially of the nervous system, are not proportionate to the height of the temperature. Thus in influenza, symptoms of toxæmia and general depression may be very marked when the temperature is little raised, and it is known that the earliest signs of structural damage to the cells of the body met with in fever, e.g. cloudy swelling, fatty degeneration, etc., are the effects of toxic action rather than of the high temperature. In any given case, however, both factors which we have mentioned are present in varying degree, and the pyrexia in itself becomes a formidable danger when it increases towards the level of hyperpyrexia.

Other Causes of Pyrexia. Abnormally high temperatures are met with in conditions other than fever as above defined, and of these the two most important are *heat-stroke* and *lesions of the nervous* *system.* It may be noted that in all cases where the temperature is abnormally high, the *regulating mechanism* may become defective, and then there is a tendency for the pyrexia to raise the production of heat and the temperature to a still higher level; this factor apparently plays an important part in hyperpyrexia. Further, while in consequence of the regulating mechanism the temperature of a normal individual may be little raised in a very hot atmosphere provided that it is dry, the regulation may fail when the atmosphere is moist. For example, Haldane found that as soon as the wet-bulb temperature rose to 88° F., the temperature of a normal individual at rest began to rise, and if there were any muscular exertion at the same time, the rise became marked. The pyrexia was accompanied by marked increase of pulse rate, tendency to dyspnœa, and general discomfort. Failure of regulation in this way is an all-important feature in heat-stroke. This condition is met with amongst soldiers on the march, stokers, workers in hot moist mines, etc., and in its production a warm, moist, and stagnant atmosphere, excess of clothing, and severe muscular exercise are favouring factors. The increased temperature gives rise to further heat production with deficient regulation. In heat-stroke the temperature may rise to a great height, whilst the pulse becomes rapid and feeble; there may be dyspnœa, delirium, and convulsions, and death may follow. In some cases symptoms of collapse or heat exhaustion are more prominent than the high temperature. When recovery from heat-stroke takes place there may be symptoms of damage to the nervous system for some time. The condition of sunstroke, in which again hyperpyrexia may develop, is often described as being due to the direct effect of the sun's rays on the central nervous system; but some authorities have questioned this interpretation and regard the condition as a variety of heat-stroke.

Pyrexia, often amounting to *hyperpyrexia,* is met with in certain lesions of the central nervous system, and it has been supposed that here it is the result of interference with a special heat-regulating centre or centres. Lesions occurring naturally and also experimental puncture in the region of the basal ganglia, have been found to give rise to abnormally high temperature, but it is to be noted that lesions of the cortex and of the pons are sometimes associated with a like condition. The chief heat centre is believed by many authorities to be in the corpora striata, but more recently evidence has been brought forward that it is below the thalamus. The nervous mechanism involved in the maintenance of a normal temperature is complicated, and is concerned both with heat loss and heat production. The former is fairly well understood, but little is known with regard to the relation of the nervous system to increased metabolism and the manner in which control is exerted. It is thus likely that lesions in different parts may disturb the regulation of temperature, while, at the same time, certain centres may be of special importance. The pyrexia resulting from puncture has been called *neurogenic*, and it appears to depend chiefly on excessive metabolism of carbohydrates, especially in the liver. Lusk has suggested that it has pretty much the same relation to fever as puncture glycosuria has to true diabetes.

A certain degree of pyrexia accompanied by general systemic disturbance may be produced by the injection of foreign proteins, e.g. milk, peptone, etc., and especially by dead bacteria. The resulting condition is known as *protein shock*. Advantage has been taken of this fact in the treatment of various chronic diseases, the general reaction produced having in some cases a favourable effect. Such treatment has been called ‘non-specific therapy.’ Campbell, for instance, obtained good results in chronic rheumatism by means of dead typhoid bacilli. It has been supposed that in such cases there is a non-specific stimulation by the dead bacteria of the formation of antibodies, but for this view there is not sufficient evidence. The favourable effect in general paralysis by malarial infection may be an example of similar nature, though in this case living organisms are concerned.

It may be added that in the case of some tumours, quite apart from the presence of bacterial infection, a certain amount of pyrexia may be present and this probably arises from absorption of products of protein disintegration or of abnormal metabolism. A similar occurrence is met with in connection with necrosed tissue, for example in cardiac infarctions (p. 340). Pyrexia may be produced also by certain drugs.

CHAPTER VI

TUMOURS[1]

In previous sections we have seen examples of cell proliferation and growth of tissues in the process of repair, in response to irritation, and as a hypertrophic process, and we have been able to recognise in such growth an adaptation to a particular end. In other words, the growth has been intelligible, and, up to a point, capable of explanation. Tumour growth is, however, in a different category. In the case of a tumour or neoplasm, the growth is not only excessive but it is usually progressive, apparently purposeless, and it proceeds without regard to the surrounding tissues or the requirements of the organism as a whole. Whilst forming a part of the body, a tumour is not regulated by its ordinary laws; it grows apart, as it were, and independently. Accordingly, it is spoken of as *autonomous* new growth; and this autonomy may be regarded as the characteristic feature of a tumour. When the relations of tissues are disturbed by injury or otherwise, there follows not only the process of repair, but an attempt to restore the normal relations, and cells or tissues which are no longer required undergo absorption and disappear. A tumour, on the other hand, disregards normal relationships, and displaces or infiltrates the surrounding tissues. It thus behaves like a parasite, drawing nourishment from the body, but subserving no useful function.

The blood vessels of a tumour which are, of course, continuations from the vessels of the host, undergo increased formation in relation to the growth of the tumour. In simple tumours the vessels are well formed, though the walls of the arteries are often deficient in muscle, while in the malignant growths, especially in sarcomata, there is an abundant formation of thin-walled vessels. The growth of the tumour, however, is not infrequently in excess of the blood supply, and accordingly degeneration and necrosis frequently occur. The results of experimental transplantation of tumours in animals clearly show that the cells of the tumour stimulate in some way the formation of blood vessels in the new host, and the vascular features of the original growth may be produced in the growth which results from transplantation. Vascular development may thus be regarded as in most cases secondary to the growth of the tumour.

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[1] For a detailed account of tumours, with references to literature, the student is referred to *Neoplastic Diseases*, by J. Ewing, Philadelphia and London, 4th edition, 1940; *The Pathology of Tumours*, by E. H. Kettle, 2nd edition, London, 1925; *Tumeurs*, by P. Masson, Paris, 1925; *Debatable Tumours in Human and Animal Pathology*, by W. T. Harvey, E. K. Dawson 2nd I. R. M. Innes, Edinburgh, 1940.

Classification. Tumours show an extraordinary variety of structure, and may originate from any tissue of the body at some stage of its development. Thus, for example, while there is no evidence that a tumour can spring from adult nerve cells, it may do so from embryonic nerve cells or neuroblasts, at an early stage of their development. And although tumours most frequently arise from the tissues most active in repair—ordinary connective tissue, bone, epithelium of skin and mucous membranes, etc.—there occur also growths whose origin can be clearly traced to highly specialised cells such as those of the liver, thyroid gland, adrenal, etc. Tumours may thus, first of all, be classified on a purely *histological* basis, that is, according to the *nature and origin* of their cells. The particular kind of cell by whose proliferation a tumour is formed is often spoken of as the 'type cell'.

Again, tumours differ according to the *stage of development* of the particular tissue or tissues of which they are composed. In some, the constituent tissue is fully developed, closely similar structurally to that found in the adult body, although its arrangement is irregular or atypical. Thus there are tumours composed of fibrous tissue, of cartilage, of non-striped muscle, etc. Other tumours are essentially of cellular character, and the cells do not go on to produce the features of the adult tissue; they remain more or less undifferentiated, their activity is chiefly proliferative. This is readily appreciated in the case of the cellular connective tissue tumours—the sarcomata—which are usually comparatively soft and rapidly growing. But it holds also in the case of epithelial growths, such as scirrhous cancer, where there may be induration and actual shrinking. For the tumour is really composed of proliferating epithelial cells; whilst the hardness and contraction are due to the growth of the stroma, which is not an actual part of the tumour, but is the result of irritation of the connective tissue by the invading epithelial cells.

This second principle of classification accordingly gives us the two main classes of *tissue tumours*, and *cellular tumours*, and the division is of great importance, as it corresponds with the two main clinical groups of *simple* and *malignant* growths respectively. Various attempts at exact classification have been put forward by different writers, but most of them are based on these two main principles—the kind of tissue of which they are composed, and the stage of its development. Further, these principles correspond with the two important questions which the pathologist has in his mind, in the examination of any particular growth, viz.: 'What is the origin of the growth?' and 'What will be its effects?' that is, 'Is it of simple or of malignant nature?' Other matters, such as its relation to embryonic layers, are no doubt of interest but they are of subsidiary importance. Theoretically, then, from every kind of cell in the body a tumour may spring, and its tissue may be either of adult type or may remain of cellular character—it may be simple or malignant. And we may say that the theoretic possibilities have been observed to occur actually with few exceptions. It must also be recognised that while most tumours fall readily into one or other of the two main groups—simple and malignant—tumours of intermediate structure and character also are met with, and it may be impossible to assign definitely a place to a given example. As will be shown later, there are all degrees of malignancy just as there are all grades in structure.

We thus divide the tumours originating from different tissues primarily into two main groups, viz.:

(A) Histiomata or tissue tumours.
(B) Cytomata or cellular tumours.

This corresponds with the main classification adopted by Powell White, and it appears to be both justifiable on scientific grounds and also convenient for practical purposes. In some growths, however, there is a great complexity of structure and several distinct tissues may be represented, that is, they are *mixed tumours*. In one type undifferentiated cells are present, and these can be seen developing in various directions and forming different tissues. Such a growth is manifestly derived from multipotent cells which occur in an early stage of development of the embryo, and to this growth the term ‘blastocytoma,’ as suggested by Powell White, may be conveniently applied. In another type, the tumour is composed of fairly well-formed, though irregularly arranged tissues, and these may represent all three germinal layers. The term *teratoma* is usually applied to growths of this class. The characteristic features of these mixed growths will be described later, but it may be noted here that in many instances a teratoma is not a true tumour, in the sense of exhibiting progressive and autonomous growth; it is simply a mass of misplaced and mal-arranged tissues. A tumour in the strict sense may, however, arise from one or more of its component tissues.

Tumours are now often classified according to the cell or tissue from which they take origin, simple and malignant growths being recognised in connection with each variety. Either principle of classification has its advantages but we have thought it better to retain the older classification.

Effects of Tumours. These are very various and many of them can be readily understood. The presence of a mass of growing tissue of whatever kind may lead to pressure on various important structures, e.g. on blood vessels (especially veins), nerves, tubes and organs, and the usual results will follow. In the case of malignant growths such structures are often infiltrated and destroyed, and their function is interfered with; and, further, the contraction of tissue which occurs in a scirrhous carcinoma often produces obstructive effects, e.g. stenosis of pylorus, intestine, bronchi, etc. The tissues of tumours have two main features, which are of importance in relation to the effects produced by them. On the one hand, they are readily injured and have little or no power of repair, and, on the other hand, they have little resistance to bacterial invasion. Thus a tumour in relation to skin or a mucous membrane often becomes ulcerated, and, as growth goes on, extensive destruction follows. This is seen especially in the case of malignant growths, but a simple tumour also, e.g. a myoma in the cavity of the uterus, may be extensively ulcerated. Ulceration often involves blood vessels, and thus serious and sometimes fatal hæmorrhage may result. Soft cancers in the stomach and elsewhere may be extensively invaded by bacteria and undergo extensive sloughing, and there is no doubt that the absorption of bacterial toxins in such conditions plays a very important part in the production of the anæmia and wasting which are often such prominent features. There still remains the question, whether by the tumour itself any substances are produced which aid in bringing about malnutrition or cachexia by their toxic action, that is, apart from the withdrawal of nourishment by a rapidly growing tumour. The occurrence of pyrexia can usually be ascribed to secondary bacterial invasion, but may occur apart from it and may be due to absorption of products from dead and autolysed tissue. It is hardly possible to give a decided answer to the question, but it seems to us that the main effects seen in cases of malignant disease are due to the factors above mentioned, and that effects of auto-intoxication proper are of a subsidiary nature. The above is a mere sketch of some of the main results of tumours; others will be exemplified in the account of the growths in various organs.

Metabolism of Tumours. Observations have been made on the metabolism of tumour cells as compared with normal cells. The most important results are those of Warburg[1] and his co-workers, which show that the cells of malignant tumours possess a remarkably high degree of glycolytic function, as shown by the amount of lactic acid formed from glucose without oxidation. Under anærobic conditions this amount is several times that formed by normal adult tissues, though embryonic tissues produce a fair amount. Under aerobic conditions, however, the amount of lactic acid formed by malignant cells is only slightly reduced by the respiration, whilst normal tissues have almost a pure respiratory metabolism—that is, oxidation of glucose to form carbon dioxide and water. A cancer cell can live and exert its glycolytic function under anærobic conditions for a considerable time; as soon as it dies the function stops. Normal cells, on the other hand, rapidly die under anærobic conditions. Warburg points out that when there is lack of oxygen, cells without glycolytic function must perish, whilst cells with glycolytic function may survive. A chronic state of oxygen deficiency will thus tend to develop cells with marked glycolytic function just like malignant tumour cells. This might account for the metabolic peculiarities of the latter, but does not explain their indefinite growth and infiltrating properties.

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[1] See *The Metabolism of Tumours*, by O. Warburg, London, 1930.

Further observations have shown that the nature and magnitude of cancer metabolism are not so characteristic as Warburg supposed. Crabtree, for example, has found that abnormally proliferating tissues, *e.g.* in response to bacteria or viruses, may present the same peculiarities. What is the feature special to the cancer cell is the *permanent* character of the disordered respiration, this being passed on from one cell generation to another. Thus it is a feature to be associated with its properties of uncontrolled and limitless proliferation ; it is a manifestation of these properties but is not to be regarded as their cause.

The activity of tumour cells, as has already been stated, is essentially directed towards proliferation, and as a rule there is no evidence of increased functional activity. An exception to this, however, is seen in the case of certain tumours of the endocrine glands, e.g. pituitary, parathyroids, islands of Langerhans, etc. In these the characteristic results which follow give clear evidence of the production in excess of the particular hormone. Such growths are chiefly of adenomatous types and it is sometimes difficult to decide whether they are to be regarded as true tumours or as functional hyperplasias. They will be described later in the account of the endocrine glands.

The various factors concerned in the *causation* of tumours will be more conveniently considered after the different varieties of growths have been described.

I. SIMPLE TUMOURS—HISTIOMATA

These are composed chiefly of fully developed tissues ; such are met with in the adult body, e.g. fibrous tissue, cartilage, muscular tissue, etc. They are usually rounded or lobulated in form and well defined, being not infrequently enclosed within a distinct fibrous capsule. They displace the surrounding tissues and produce atrophy by pressure, but no infiltration occurs ; nor are secondary growths formed. It is to be noted, however, that simple tumours are not infrequently multiple, but in such a case each tumour represents an independent focus of growth. Blood vessels grow in relation to the tumour tissue, and are usually well formed, though the arteries are often deficient in muscle fibres.

It appears unnecessary to subdivide the simple tumours or histiomata, but it may be noted that the varieties described below take origin from the following tissues, namely :

(*a*) the *mesodermic connective tissues and muscle*—fibroma, osteoma, chondroma, myoma, etc. ;

(*b*) *blood vessels and lymphatic vessels*—hæmangioma and lymphangioma;

(*c*) the *various epithelia*—papilloma and adenoma; and

(*d*) the *neural ectoderm*—glioma and ganglio-neuroma.

It will be found later that malignant growths or cytomata correspond to all these types.

Fibroma. This tumour, which is composed of fibrous connective tissue, varies considerably in density, and thus hard and soft varieties are spoken of. The hard fibroma is usually of small size and of very dense consistence; on section, it is pale, and may show a wavy marking, which has been compared to watered silk. Microscopically, it simply shows broad and somewhat hyaline bands of connective tissue running in a more or less irregular manner and containing relatively few cells (Fig. 108). The soft fibromata may reach a considerable size (Fig. 110); they may have a pinkish colour and may be of somewhat succulent character. The connective tissue fibres are seen on microscopic examination to be thinner and arranged in whorls or in a somewhat radiating manner, whilst cells may be fairly abundant (Fig. 109).

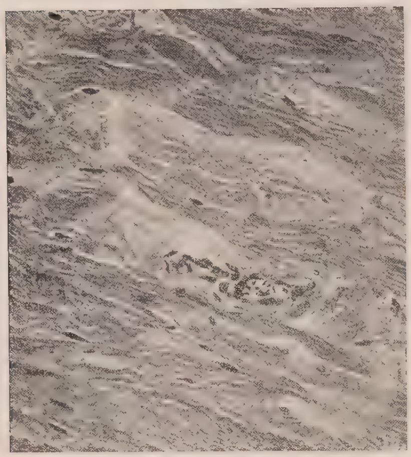

FIG. 108.—Hard Fibroma showing thick collagenous Fibres with few Cells. × 200.

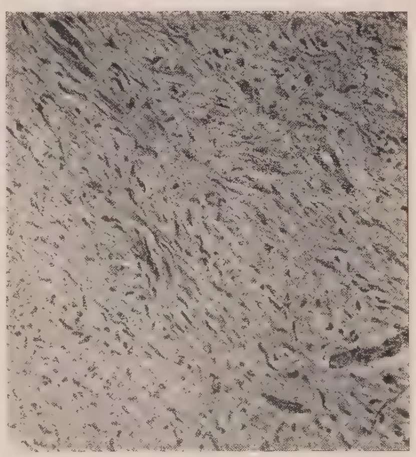

FIG. 109.—Soft Fibroma showing relatively cellular structure. × 200.

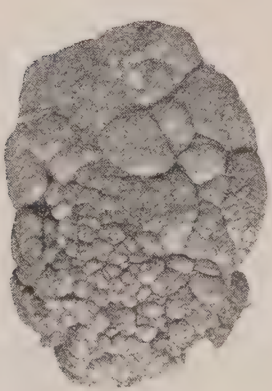

FIG. 110.—Lobulated Fibroma re-moved from Buttock. × $\frac{2}{3}$.

It is to be noted that there is no sharp line between the hard and soft varieties, and further that the latter pass by intermediate stages into the sarcomata. Moreover, variations in type of structure may be met with in the same growth. A tumour of intermediate character was described by Paget under the name of 'recurrent fibroid.' While its histological features point to its being benign, it tends to recur after removal and may ultimately assume sarcomatous characters. A fibroma may be the seat of myxomatous change at places—myxofibroma, or may contain fat—fibrolipoma ; when in connection with bone, and sometimes even when quite unconnected with the skeleton, it may be the seat of calcification or partial ossification. Fibromata are commonest in the connective tissue of the skin, fasciæ, periosteum, sheaths of nerves (neurofibromata), and they are met with also in internal organs, e.g. in the kidneys or ovaries, reaching sometimes a large size in the latter organs. In the skin, they are often multiple and may be in considerable numbers, constituting the condition of *molluscum fibrosum*, or *multiple fibromata* of the skin ; sometimes there are also localised areas of diffuse and irregular thickening. In most cases of this condition, though possibly not in all, the tumours grow in connection with the sheaths of the nerves and are really neurofibromata. The condition was fully described by von Recklinghausen, and is often named after him (p. 803).

The term *keloid* is applied to tumour-like nodules or irregular thickenings, which tend to form in certain individuals after trauma, especially in connection with cicatrices ; for example, those following burns. The keloid tissue is very dense, and like scar tissue contains very few blood vessels. The tendency to the occurrence of keloid seems to depend upon some individual peculiarity or idiosyncrasy, and in some cases keloid formation has been found to appear in connection with very slight wounds, for example those made in the piercing of the lobes of the ears for ear-rings. It is quite likely that, in individuals with this peculiarity, well-marked nodules which appear as tumours are examples of this peculiar reaction to injury. Keloid growths may be surgically removed sometimes, if not often, without re-formation.

Myxoma. In its pure form myxoma is comparatively rare, but myxomatous tissue is often associated with other tissues in various growths, both simple and malignant—myxo-adenoma, myxochondroma, myxosarcoma, etc. A myxoma is composed of somewhat translucent tissue, which has often a brownish colour owing to the occurrence of hæmorrhage. The growth is well encapsulated and may occasionally reach a considerable size. On microscopic examination it shows the ordinary features of myxomatous tissue as met with in the fœtus, the cells being of a somewhat stellate form, with branching processes embedded in a clear mucoid matrix (Fig. 111). Myxomata occur chiefly in the subcutaneous tissue, occasionally in the mamma, in internal organs, e.g. the heart, and in the subperitoneal connective tissue. They grow also from the sheaths of nerves, thus constituting another variety of false neuroma; occasionally a myxoma of this nature may reach a large size and undergo central softening. The myxomatous tissue in some mixed tumours of congenital origin may be regarded as representing a persistence of fœtal tissue, and some writers regard all true myxomata in this light. In some growths, however, the myxomatous tissue is clearly formed by metaplasia from another tissue, e.g. fibrous tissue or cartilage. Myxomata are usually quite simple growths, but myxosarcomata and transitional forms also occur. The common mucous polypi of the nose, which are met with as tense oval growths with smooth surface and jelly-like consistence, are not to be regarded as true myxomata, but simply consist of extremely œdematous submucous connective tissue.

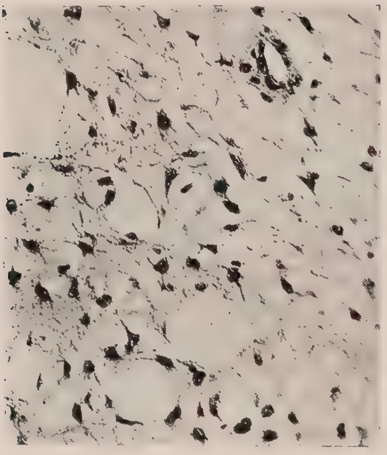

Fig. 111.—Myxoma of Breast, showing branching Cells in clear Matrix. × 200.

Lipoma. The lipoma is a simple tumour composed of ordinary adipose tissue. Around the blood vessels, round or oval cells are usually to be seen, and it is by the proliferation of these and their subsequent infiltration with fat, that the tumour increases in size. A lipoma is usually a somewhat rounded mass, well demarcated, projecting from the skin, and in some cases pedunculated. It sometimes reaches a considerable size, and may have blunt projections which pass into the tissues around. Not infrequently multiple tumours are present and occasionally they are symmetrical. The origin of lipomata seems to have a certain relation to irritation and pressure, as they are commonest over the shoulders and buttocks. They occur also within the abdomen, especially in connection with the omental fat and appendices epiploicæ, but also in the subserous and submucous coats of the stomach and bowel; occasionally, though rarely, in the internal organs, where they may be of congenital origin. An interesting fact in connection with these tumours is that, should the patient become emaciated, the fat in the tumour is not utilised, being outwith the general metabolism of the body. In a lipoma there may be areas of fibrous or myxomatous tissue—the tumour being then a fibrolipoma or myxolipoma respectively; occasionally there are areas of calcification. We have seen sarcoma develop in connection with lipoma, but such an occurrence is very rare.

Fibro-endothelioma. The best-known example of a simple tumour in which endothelium is a constituent is met with in connection with the membranes of the brain or spinal cord. It forms a firm or even hard mass which projects inwards and may sometimes reach a large size (p. 786). Not infrequently, there is a considerable amount of calcification in the growth, hence the term *psammoma* or *brain-sand tumour* has been applied, but it is to be noted that lime salts may be deposited in other varieties of intracranial tumour, e.g. in a papilloma growing from the wall of the ventricles. On microscopic examination, a fibro-endothelioma is found to be composed of a fibro-cellular tissue which has a somewhat whorled appearance, and here and there the cells come to be concentrically arranged, and then undergo a hyaline change which is followed by calcification (Fig. 112). In this way, a large number of spherical calcified particles are produced. The walls of blood vessels also may undergo hyaline change followed by thrombosis and calcification. The tumour is evidently composed of fibrous tissue elements between which there are endothelial cells, and, in some instances, the latter may be specially numerous and prominent, or even acquire invasive characters, in which case a cellular endothelioma results. The tumour is of importance from the practical standpoint as it is fairly common, and when accessible it is often capable of being successfully removed. Fibro-endotheliomata of the cerebral and spinal meninges are now usually spoken of as *meningiomata*. Their characters are described in greater detail later (p. 786).

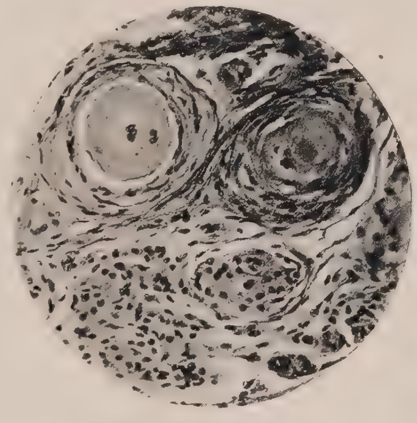

Fig. 112.—Fibro-endothelioma or Meningioma of Dura Mater, showing Fibro-cellular Masses with concentric arrangement and formation of Hyaline Bodies. × 150.

Chondroma. Tumours composed of hyaline cartilage oftenest arise from the epiphyseal lines of bones. The commonest sites are the small bones of the hands and, less frequently, of the toes ; and there they are often multiple. They form rounded firm masses which may reach a considerable size, and, on section, are seen to be composed of islets or nodules of cartilage enclosed by ordinary connective tissue (Fig. 113), which may be fairly vascular. The connective tissue next the cartilage acts as a perichondrium, and it is by proliferation of its cells and subsequent metaplasia that the cartilage increases in amount. The substance of the tumour shows the ordinary features of hyaline cartilage, but the cells are less regular in size and shape (Fig. 114). Occasionally islets of spongy bone may be incorporated in the tumours. Chondroma, which sometimes reaches an enormous size, occurs occasionally in connection with the ilium, and we have seen a similar growth in the scapula. These large tumours usually undergo a considerable amount of degeneration and softening in their central parts, and there is often extensive myxomatous change. The examples given are usually of quite simple nature, but there occur also cellular chondromata—chondrosarcomata—in connection with the ends of the long bones. These tumours are often highly malignant (p. 230). Hyaline cartilage is met with as a constituent of various mixed tumours, e.g. in the parotid, testicle, etc., and chondromata may occasionally be found apart from normal cartilaginous or osseous structures.

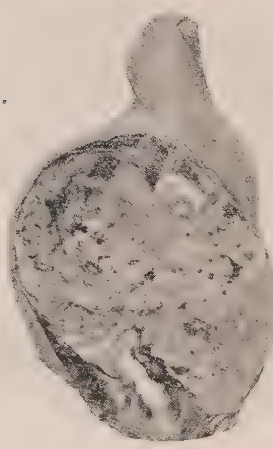

Fig. 113.—Chondroma of Finger shown on section.

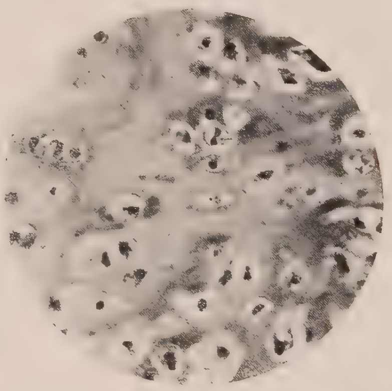

Fig. 114.—Chondroma, showing Cells irregularly arranged in Hyaline Matrix. × 250.

Osteoma. Whilst bony outgrowths or osteophytes are of common occurrence in connection with chronic inflammatory conditions of bone and certain diseases of joints, true osteoma is a comparatively uncommon tumour. Two varieties are usually distinguished, viz. a *hard or ivory osteoma* and a *spongy or cancellous osteoma.* Occasionally the tumour occurs in the central parts of a bone, but much oftener it grows outwards, forming a projection commonly spoken of as an *exostosis.* Two varieties are also to be distinguished as regards the mode of formation of the bone. In one variety, the tumour is covered by a layer of cartilage, and enlargement follows by a process like ordinary ossification in cartilage. Such a tumour occurs in the region of the epiphyseal lines. An example of this is met with on the dorsal aspect of the last phalanx of the big toe, where the growth raises the nail of the toe ; it is called a sub-ungual exostosis. In the other variety the tumour is simply covered by periosteum. Osteoma is met with in the bones of the skull ; the frontal bone is a not uncommon site and the tumour is often of the hard or ivory type. It occurs in connection with the bones of the face, and may project into the orbit or antrum of Highmore. It is met with also in the long bones, although there it is relatively rare. Abnormal bone formation, which cannot be regarded as of the nature of true tumour, occurs in a number of situations, for example, in the dura mater, and occasionally in the lungs; and there is the peculiar condition called *myositis ossificans*, in which much bone is formed in the tendons and substance of the muscles. Bone formation occasionally occurs also in mesial abdominal scars. In these cases, the bone formation seems to be of the nature of metaplasia.

Odontoma. The term is applied in a general way to any tumour-like mass developing in connection with the tissues which form the teeth. Such a growth may arise at various stages of development, and may consist of one or several tissues; accordingly odontomata present considerable varieties of structure. We can mention only a few in illustration. Sometimes the tooth follicle forms a cyst, in the interior of which one or more teeth may be formed—*dentigerous cyst*; occasionally the cyst may contain a large number of imperfectly developed teeth or denticles. In the cyst wall lime salts are often deposited or formation of bone occurs. In other cases an odontoma consists of various structures containing enamel and cement irregularly fused together and sometimes forming a hard irregular mass; the term *composite odontoma* is applied to such a structure. In other cases again, the growth is of epithelial nature and is composed of masses and anastomosing strands of epithelial cells (Fig. 115). Those at the periphery are usually columnar in type and are believed to represent enameloblasts, whilst the cells within are of more rounded or irregular form. The cell masses may be solid, but not infrequently the central portions undergo softening so that cysts are formed, which are often multiple. Such a growth was ordinarily called *epithelial odontoma*, but recently the term *adamantinoma* has

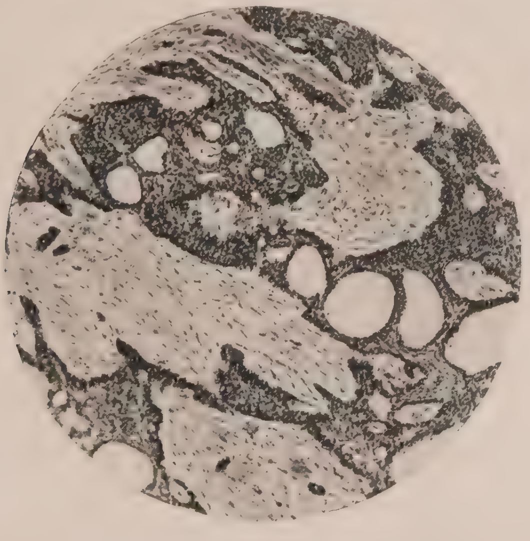

FIG. 115.—Section of Adamantinoma showing Spaces lined by Epithelium and solid Masses of Epithelial Cells. (Dr. G. McCallum.) × 70.

come into use. According to one view, such growths take origin from an enamel organ, whilst according to another they are derived from small masses of epithelial cells—'paradental remains'—which occur normally in the fœtus in the region where the teeth are being developed. Such epithelium is, however, of nature homologous to that of the enamel organ. Whilst adamantinomata often behave as simple growths, especially the cystic varieties, the more solid types not infrequently present the invasive and destructive properties of epithelioma; occasionally also malignant change takes place in the stroma.

Myoma. There are two varieties of myomata, viz. the leiomyomata, composed of non-striped muscle fibres, and the rhabdomyomata, in which striped muscle fibres are constituent elements. The latter form is, however, so rare that the term myomata without qualification is often used simply to signify leiomyomata.

The **leiomyomata** are composed of fasciculi of non-striped muscle cells, which are arranged in a more or less parallel manner within the bundles, whilst the latter are arranged in a whorled manner (Fig. 116). A small amount of supporting connective tissue runs amongst the individual fibres, whilst broader bands separate the bundles. The proportion of connective tissue to muscle fibres varies much in different specimens, and when the fibrous tissue is abundant, the term *fibromyoma* or *fibroid* is applied. The tumours are usually of a firm consistence and rounded form, and, on section, have a pinkish colour and a characteristic concentric marking or whorled appearance, owing to the arrangement of the fibres (Fig. 117). Leiomyomata are essentially simple growths, but sarcoma may develop in connection with them, and may originate from the muscle cells. This tumour, which is called a myosarcoma, is, however, of rare occurrence. The commonest site of myomata is the uterus, in which they are often multiple. They occur also in the ovaries,

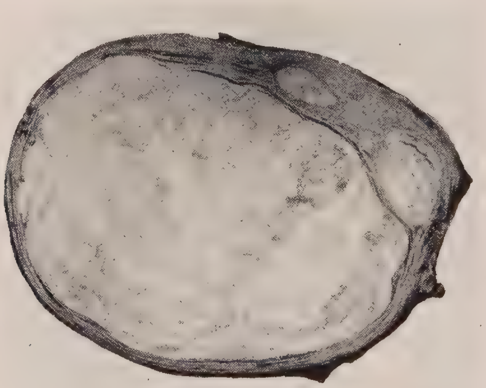

FIG. 116.—Transverse section of Leiomyoma of the Uterus, showing the characteristic marking. × $\frac{3}{4}$.

prostate, bladder, alimentary tract, etc., but are relatively rare. Occasionally small myomata are found in the skin, and it has been supposed that they may be derived from the walls of blood vessels or the *erectores pilarum.*

The leiomyoma of the uterus is extremely common, and may sometimes reach a very large size. Although it is usually of a firm consistence, the stroma may become œdematous and mucoid softening may take place, or, in other cases, there may be hæmorrhage with autolytic softening—'red softening.' Myomata usually cease to grow at the menopause, and a considerable amount of involution with decrease in size is common. The muscle fibres then atrophy, and form a smaller proportion of the growth. Fatty change may occur, and may be followed by calcification. A tumour may be thus converted into a hard stony mass or 'womb-stone,' and it is interesting to note that, when it is sawn across, the peculiar concentric markings may still be visible on the cut surface. Further details with regard to uterine myomata will be given later (p. 876).

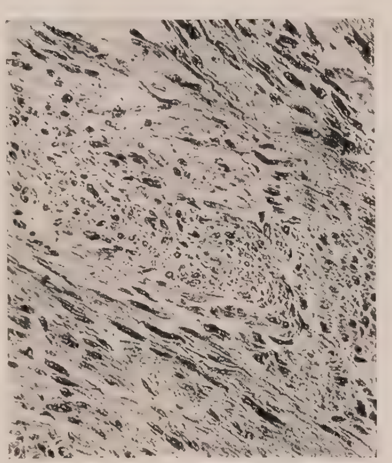

FIG. 117.—Leiomyoma.

The muscular bundles are seen in longitudinal and in transverse sections; the tumour is more cellular than usual. × 200.

Rhabdomyoma. This is a tumour of rare occurrence, in which imperfectly formed striped muscle-cells or myoblasts are present. It occurs especially in connection with the genito-urinary tract, less frequently in the alimentary tract, and occasionally in the skeletal muscles. A form of rhabdomyoma has been observed also in the cardiac muscle (p. 371). The growth is probably always of congenital origin, but it is not possible to explain why it occurs in parts where non-striated muscle but no striated muscle, is present. The tumour has generally the appearance of a fairly firm sarcoma in which many of the cells have the usual characters while others are greatly elongated and show transverse striation especially in the peripheral portion of the cytoplasm, the nucleus or nuclei being central in position. Sometimes fairly well-formed bundles of thin fibres are present. The tumour may remain localised and reach a considerable size, but not infrequently it presents invasive characters and metastases may be produced (Fig. 142). Striped myoblasts may be met with also in certain teratoid tumours along with cartilage, glandular epithelium, etc. A tumour of this kind occurs sometimes in the region of the kidney, and in it are present both muscle elements and others representing kidney structures (p. 699).

Hæmangioma. A hæmangioma consists of a mass of blood vessels, atypical or irregular in arrangement and size. A corresponding growth, lymphangioma, is composed of lymphatic vessels similarly altered; but as this is rarer, the term angioma is often used as synonymous with hæmangioma. Varieties of hæmangiomata are distinguished according to the predominant type and arrangement of vessels. In the *plexiform* angioma, the dilated vessels retain their ordinary form as coiled tubes; the vessels may be chiefly capillaries—*capillary angioma or nævus*; or they may be mainly composed of large veins—*venous angioma or nævus*. There is no hard and fast line, however, between these two types, as in most instances both kinds of vessel are involved, though one to a special degree. The other type of angioma is the *cavernous*, in which the tumour is composed of a series of intercommunicating vascular spaces, separated by a definite stroma, the arrangement resembling closely that of an erectile tissue (Fig. 118). Capillary angiomata occur most frequently on the face, although they are met with also on other parts of the body. They may be comparatively small, scarcely raised above the surface and of crimson tint; or, on the other hand, they may involve a considerable area, when they are usually somewhat elevated and of darker colour.

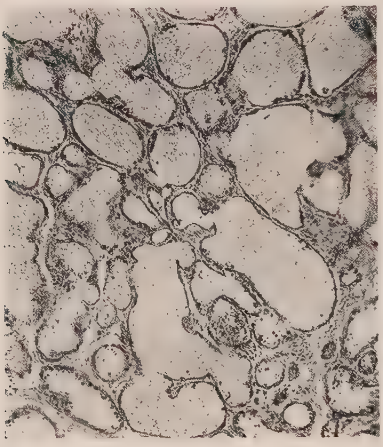

FIG. 118.—Cavernous Angioma of Subcutaneous Tissue, showing large intercommunicating Spaces filled with Blood. × 80.

Then transitions are met with to angiomata of venous type, these forming more distinct projections and being of a purple colour. Angiomata occur also in the mucous membrane of the mouth, in the subcutaneous tissue, and in various internal organs, kidneys, intestines, brain, etc. In the liver, angiomata of the cavernous type are comparatively frequent. They are of a dark purplish hue and are usually well demarcated from the adjacent tissue (Fig. 119). They may be single or multiple.

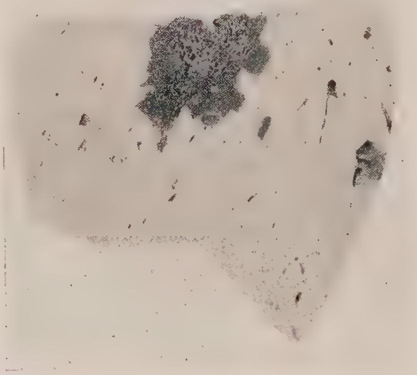

FIG. 119.—Cavernous Angioma of Liver.

The capillary angiomata are essentially composed of a mass of capillaries with well-formed interstitial stroma; they are often badly defined at their margins, and their vessels may be mixed with other tissues. Their endothelial cells are usually plumper than those of normal vessels, and they may have an almost cubical form (Fig. 120).

Angiomata are usually due to abnormalities in the process of development; in fact, this is probably always the case. The vascular territory of each angioma seems to be relatively separate and independent, as it has been found by injections that there is little or no connection with the surrounding vessels. The angiomata often remain little altered in size, and are thus to be regarded as abnormalities in growth rather than as true tumours; sometimes, however, they enlarge out of proportion to the rest of the body, and this would appear to be due to increase and enlargement of their own vessels rather than to dilatation of the vessels around. Although often ill-defined at their margins, they are essentially of simple nature. Cases, however, have been met with where multiple angiomata were present in the skin and internal organs. A few instances also have been recorded where angiomata have formed numerous metastases and yet have presented the histological features of comparatively simple growths. Shennan has published a remarkable case of this kind, and has described the growth within the pulmonary vessels of endothelial tufts, which might be carried off and distributed by the blood stream to give rise to other growths. Such an occurrence is, in a way, comparable to the transplantation of papillæ from a papilligerous ovarian cyst (p. 888) or to the transplantation of portions of endometrium as occurs in certain adenomyometa (p. 879). Further, it may be mentioned that there occurs a malignant type of endothelioma whose origin is traceable to the vascular endothelium and which forms solid masses of cells—angio-endothelioma; but this growth also is relatively rare (p. 252). Tumours originating from vascular endothelium thus form an interesting group, as they present all stages from simple to malignant types.

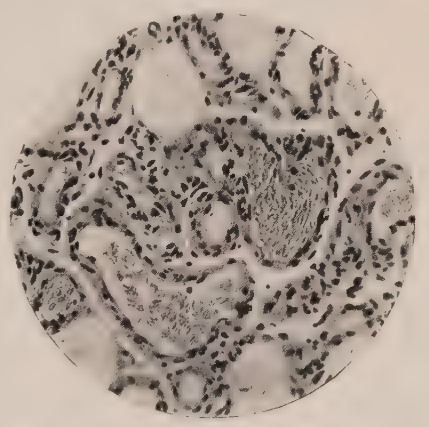

Fig. 120.—Capillary Angioma or Nævus, showing Capillary Channels containing Blood. A few fat cells, seen as clear spaces, are present. × 200.

Glomangioma. This is a special form of angioma, known also as 'glomus tumour,' which develops in connection with a glomus or arterio-venous anastomosis. In such an anastomosis a coiled arteriole, abundantly supplied with nerve fibres, communicates directly with a vein, and the arrangement is recognised as having an important function in regulating the peripheral circulation and skin temperature. Such anastomoses occur especially in the extremities, notably under the nail bed. The tumour is of simple nature, forming a small localised nodule and a characteristic feature is its painful character. In some of the cases known as 'painful subcutaneous tubercle of Wood' the condition was presumably of this nature. On microscopic examination the tumour is found to consist of two kinds of tissue variously interblended (Fig. 121). One is of cavernous type, the spaces being filled with blood and separated by fibromyomatous tissue. The other is a cellular tissue, the characteristic cells of which are of rounded or cuboidal form and are called 'myoid,' as transitions to smooth muscle fibres can be found. The growth is abundantly supplied with medullated and non-medullated fibres and the pain is apparently due to distensile pressure of the blood-containing spaces. The painfulness is not, however, in proportion to the neural content. The origin of the growth seems to be distinctly related to traumatism and it is doubtful if the condition should be regarded as a true neoplasm. It is to be noted that a small myoma of the cutis may have a similar painful character and it is possible that the two forms of growth may have a relationship in origin.

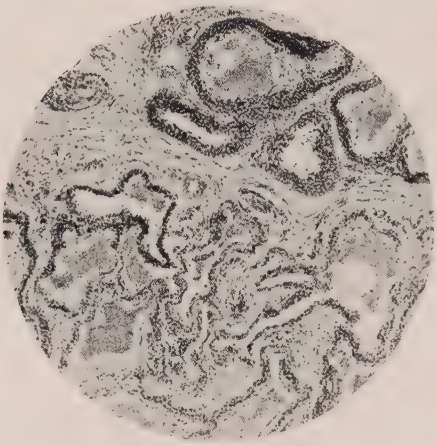
Fig. 121.—Glomangioma showing arrangement of vascular spaces. Note cellular mantle to vessels in upper part of field. (A.C.L.) × 50.

Lymphangioma. This variety, as has been stated, is derived from the lymphatic vessels, and presents a certain correspondence with the hæmangioma. It may be composed of numerous lymphatic vessels—the *plexiform* lymphangioma—but more frequently it has a *cavernous* structure. Dilatation and growth of vessels may occur as a diffuse process called *lymphangiectasis* and give rise to enlargement of a part; for instance, a condition of enlargement of the tongue or *macroglossia* may be produced in this way. Such a condition may be of congenital origin, but it is sometimes difficult to distinguish it from one resulting from lymphatic obstruction, which may be produced by chronic inflammation, para-

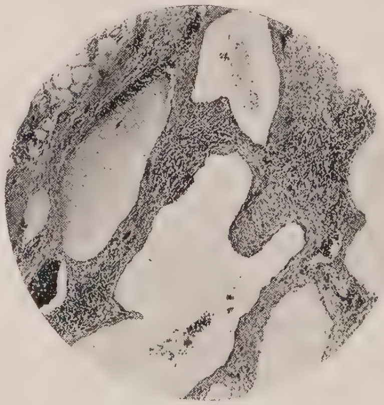
Fig. 122.—Cavernous Lymphangioma of Subcutaneous Tissue, showing intercommunicating spaces filled with Lymph, in which there are some collections of Lymphocytes. × 45.

sites, etc. The cavernous lymphangioma occurs most frequently in the skin and subcutaneous tissue, and may form a distinct swelling, somewhat ill-defined and having a doughy or semi-fluctuating character. On microscopic examination it is found to contain large intercommunicating lymphatic spaces, between which there are ordinary connective tissue and fat (Fig. 122). And an interesting point is that bundles of non-striped muscle may be present, these probably being derivatives from the muscle of the walls of lymphatic trunks. The contents of the spaces are a clear lymph, in which collections of lymphocytes are present. Sometimes effusion of blood occurs into the spaces and renders the diagnosis between hæmangioma and lymphangioma difficult. Lymphangiomata occur occasionally also in mucous membranes, in the tissues of the orbit and mesentery, and in connection with internal organs.

Sometimes the spaces in lymphangiomata undergo great dilatation, and thus a multilocular cystic mass is formed. This has occasionally been met with in the neck and in the retro-peritoneal and mesenteric tissues; it is, however, very rare. Sometimes a single cyst is formed, as in the *hygroma* of the neck, which may reach a large size and may ramify into the tissues; it may occur either in the upper or lower parts of the neck. It may be distinguished from other cysts in this region by its being lined by endothelium, e.g. from a cyst originating from a branchial cleft which is lined by epithelium.

Papilloma. Papilloma and adenoma are usually spoken of as simple epithelial tumours, but it must be recognised that in both connective tissue is a constituent element and its growth is co-ordinated with that of the epithelium. Thus in the papilloma, connective tissue always forms a definite vascular core which supports and nourishes the epithelium (Fig. 123); and, in the adenoma which grows from glandular structures, the connective tissue retains its normal relationship to the growing epithelium.

Papillomata may grow from the skin, mucous membranes, or ducts of glands, and may occur also as ingrowths in the interior of cystic tumours. The development of papillomata has often a definite relationship to chronic irritation. Thus, a mucous membrane, the seat of chronic catarrh, often becomes

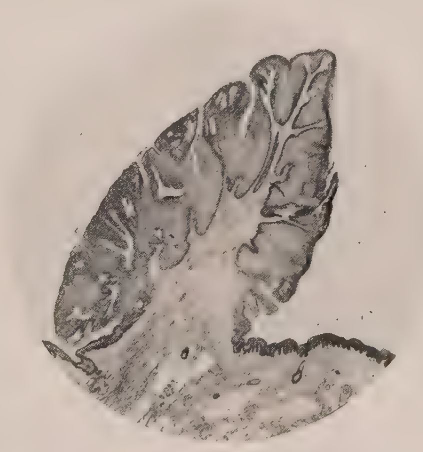

Fig. 123.—Papilloma of Skin, showing branching processes of Connective Tissue covered by stratified Epithelium. × 12.

irregularly thickened and then papillomata may develop. In the case of the skin a similar relationship is to be observed. In chronic gonorrhœa, for example, the skin around the genitals exposed to discharge may become the seat of papillomata or 'acuminate condylomata,' which vary considerably in size from simple warty projections to larger masses often broken up into fine processes or lobules. Warts in children have long been considered to be of infective nature and it has now been shown that they are produced by a filterable virus. Infective papillomata are also met with in animals. Accordingly some papillomata are clearly of reactive nature.

The stratified squamous epithelium covering the surface of skin papillomata presents variations. In some the rete Malpighii is relatively thick, but in others the stratum corneum is greatly in excess, and then the term *keratoma* is applied. Sometimes in elderly subjects, as a result of irritation, epitheliomatous change takes place in these growths.

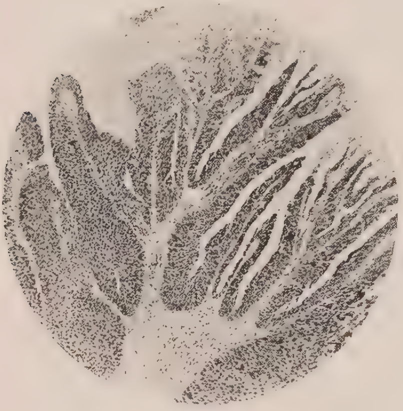

FIG. 124.—Papilloma of Bladder, showing delicate Processes with several layers of oval Epithelial Cells. × 60.

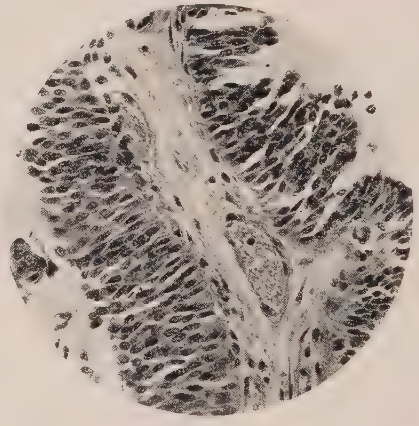

FIG. 125.—Papilloma of Bladder.

Section of a process, showing the relation of epithelium to vascular core of connective tissue. × 200.

The villous tumour of the bladder may be taken as another common example of papilloma. In this case, the epithelial processes are extremely delicate and float out readily in water, the appearance being compared to that of a sea anemone. Each process is composed of a very thin vascular core of connective tissue covered by several layers of oval or rounded cells (Figs. 124, 125), which are definitely arranged in relation to the supporting stroma. Frequently these processes become broken across and severe hæmorrhage occurs from the vascular core. It is to be noted that not infrequently the sharp line of demarcation between epithelium and connective tissue becomes broken, the cells of the tumour infiltrate the muscular wall of the bladder, and a malignant condition becomes superadded. Further, a bladder papilloma may recur after removal even when on histological examination it is apparently benign. A similar statement applies to papilloma of the larynx. In the papillomata of the stomach and intestines (Fig. 126) the covering epithelium is arranged in crypts like Lieberkühn's glands, and thus on section, a somewhat complicated appearance is presented, rather like that of an adenoma. Here again, malignant disease is apt to develop. Papillomata of the alimentary tract are sometimes multiple (p. 578). Papillomata are of common occurrence in the ducts of the mammary glands in cystic disease, and also apart from this condition (p. 902). An important example of a duct papilloma is that arising in one of the lactiferous ducts of the nipple. It is usually of somewhat rounded form and may reach the size of a small cherry; and it may give rise to sanguineous discharge or even to distinct hæmorrhage. The development of papillomata within cysts, then called proliferous or papilligerous cysts, is seen especially in cysts of the ovary and mamma.

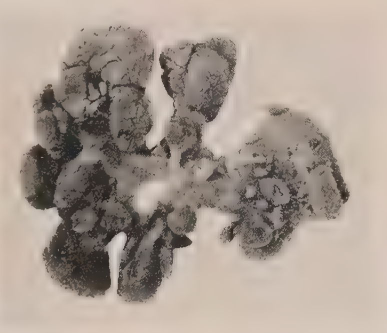

FIG. 126.—Papilloma of Rectum $\times \frac{4}{5}$.

Adenoma. The adenomata are simple tumours composed of glandular epithelium along with a varying amount of definitely arranged connective tissue. The two kinds of tissue are essential constituents. They may arise from practically any glandular organ in the body,—mammæ, ovaries, liver, adrenals, thyroid, sweat and sebaceous glands, etc. As a rule, the general structural features of the gland from which the tumour arises, are reproduced. Thus a tumour of the mamma has an acinous arrangement (Fig. 127); whereas, in an adenoma of the liver or adrenals, the cells are arranged in trabecular fashion. We consider that not infrequently adenomata take origin from glandular epithelium which has become dislocated or separated during development or at a

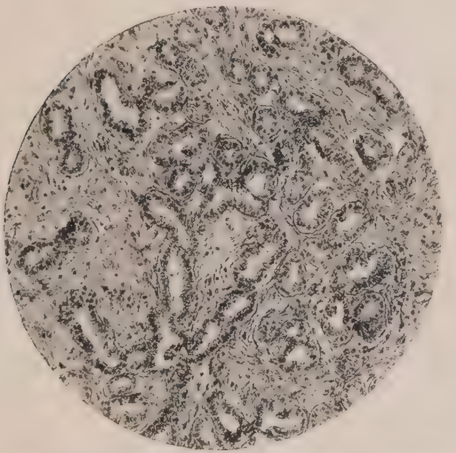

FIG. 127.—Adenoma of Breast, showing regularly formed Acini, embedded in Stroma of Connective Tissue. × 80.

later period. For example, an adenoma of the liver usually contains no bile-ducts, and the appearance is as if trabeculæ of the liver cells had become separated and had gone on proliferating indefinitely. So also, an adenoma of the adrenal appears to result from such a dislocation, just as an adrenal 'rest' does. If we consider the adenomata with acinous structure, we find that at one end of the series there are firm rounded tumours in which there is a large proportion of stroma—*fibro-adenomata*—whilst at the other end there are tumours where epithelium preponderates and is actively secreting, so that numerous cysts are formed—the *cystic adenomata.* The varieties and characters of adenomata are well illustrated in the case of the mammary growths, described and illustrated on pp. 904, 905.

The growth of the epithelium in adenomata occurs in two chief ways. In one, growth takes place by budding of the epithelium as in the process of development, and the character of distinct acini is well maintained (Fig. 127). In the other, ingrowth of papilliform projections takes place within the acini, and adjacent projections may grow together. Thus, on section, there is seen to be a large number of spaces with papilliform ingrowths, whilst the stroma is usually scanty, and in places occurs only in lines. In such a tumour the epithelial surface is very extensive, and, as the cells often secrete actively, numerous cysts are formed and the enlargement of the growth takes place rapidly. Such a type of cystic adenoma is well exemplified in the case of the multilocular cystoma of the ovary (Fig. 128). In other cystic adenomata, the wall of the cyst may become covered with pretty large ingrowths like papillomata, and the term *papilligerous cyst* is then applied. Further details as to the characters of adenomata will be given in connection with the different organs.

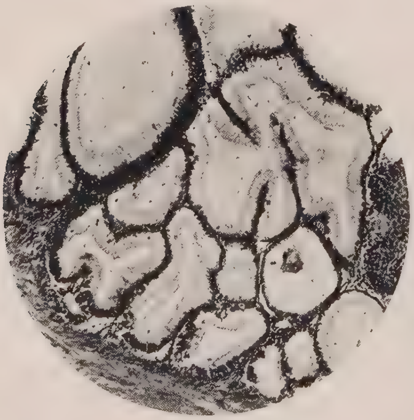

FIG. 128.—Cystic Adenoma of Ovary (Cystadenoma Pseudomucinosum), showing papilliform Processes covered by tall mucin-forming Epithelium. × 65.

Adenomata are, as a rule, of simple character, but occasionally malignant growth develops in connection with them, and border-line tumours also are met with. For example, the papilligerous cyst of the ovary may give rise to secondary growths in the peritoneum and omentum by a process of transplantation (p. 888); or, again, may become actually infiltrative.

Adenolymphoma. This is a rare type of adenoma which occurs in the salivary glands. It is met with especially in male adult life and is usually of quite simple nature. The epithelium is of tall columnar type which is arranged as small glandular acini or as cysts with numerous small papillomatous ingrowths. The stroma is lymphoid tissue with numerous germ centres. There is apparently a co-ordinated neoplastic growth of both tissues and a developmental abnormality is probably the basis of the tumour.

Glioma. Gliomata form a distinct class of tumours, as they are derived from a connective tissue of origin—*astroglia* or *macroglia*. They occur in connection with the brain and spinal cord, and show great variations in the character of the tissue. At one end of the series there are comparatively firm tumours in which there is a great development of glia fibres—astrocytoma; whilst at the other end we find soft masses of cellular type. It is to be noted that even when a glioma is of firm consistence and localised, there is no distinct capsule around it, its substance blending with the neuroglia around. The more slowly growing forms of glioma show neuroglia cells of somewhat stellate character with numerous glial fibres, the appearance corresponding generally with that of thickened neuroglia, as is seen in chronic inflammatory conditions (Fig. 129). Such a tumour is usually pale and firm or there may be considerable vascularity, and not infrequently the central parts undergo a sort of œdema with softening, so that jelly-like material or even a space containing

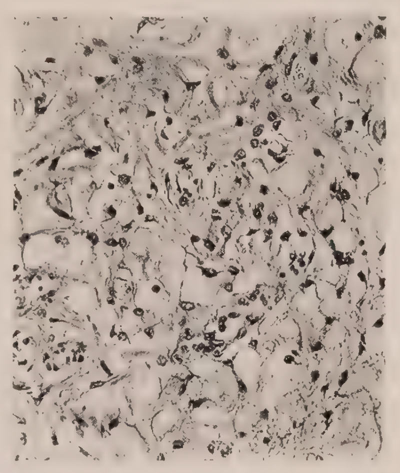

FIG. 129.—Glioma of Brain—Astrocytoma, showing Stellate Cells with delicate Fibrils. × 200.

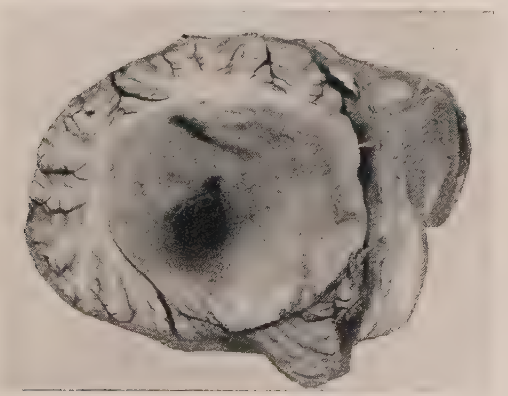

FIG. 130.—Section through Glioma (Astrocytoma) of lateral lobe of Cerebellum with central Hæmorrhage.

fluid may result (Fig. 493). Structurally it corresponds with a simple or histoid growth, though it may cause death by pressure.

Recent investigations, notably those of Bailey and Cushing,[1] have shown that the 'gliomas' form a very heterogeneous group of tumours. Most of them are of neuroglial origin and can be classified according to the stage of development of the cells. From the astrocytoma above described all stages of transition are met with up to cellular growths or cytomata, the cells often showing aberrant types. It is not possible to draw the line between simple and malignant growths of this class. This subject, however, is more conveniently considered in connection with the central nervous system.

Sometimes a diffuse over-growth of neuroglia may occur without forming any distinct tumour, and sometimes even without destroying the structure of the part to any extent. Thus the pons may become considerably enlarged whilst its structural features may be retained (p. 791). To this condition the term *gliomatosis* is applied, but transition to ordinary tumour growth is met with. The state of gliomatosis, often associated with softening and cavity-formation, is not infrequently met with in the spinal cord, especially in the cervical region ; it constitutes the condition known as *syringomyelia*, which will be described later (p. 783).

Ganglio-neuroma. A tumour to which this term can be justifiably applied is of rare occurrence, but now a large number of cases have been recorded. The tumour has been found in connection with the sympathetic system, in the abdomen, thorax, and cervical region, and in a fair proportion of instances it has arisen from the adrenal medulla. A few cases also have been recorded where such a tumour has originated in connection with peripheral nerves. Occasionally there occur in the cerebral hemispheres single or multiple nodules

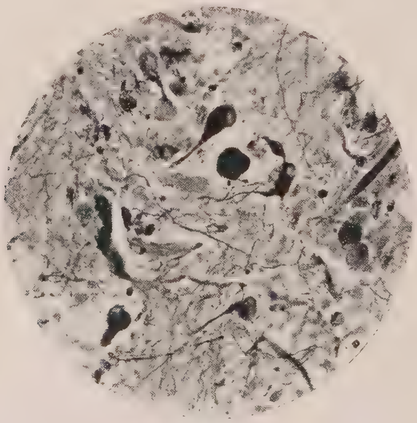

Fig. 131.—Ganglio-neuroma of Adrenal, showing Nerve Cells and Fibres embedded in well-formed Stroma. (J. S. D.)

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[1] *Tumours of the Glioma Group*, by Bailey and Cushing, Philadelphia, London and Montreal, 1926.

composed of neuroglia, in which a considerable number of nerve cells may be present, these apparently forming part of the growth ; such tumours also may be regarded as a variety of ganglio-neuroma. A ganglio-neuroma in connection with the sympathetic system may form a mass of considerable size. It is usually of firm consistence, encapsulated like a simple tumour and of rounded or irregular outline. On microscopic examination, it is found to contain well-formed ganglionic nerve cells, irregularly arranged in a finely fibrillated stroma, and also smaller cells of various forms with nuclei of the characteristic type (Fig. 131). There are usually also a large number of nerve fibres both medullated and non-medullated ; also naked axis cylinders. The growth is as a rule of quite simple character, but occasionally cellular malignant growth develops in connection with it. This is the neuroblastoma (p. 255), the cells of which resemble embryonic neuroblasts. We have here accordingly an interesting example of abnormality in the formation of the sympathetic nervous system, from which a corresponding tumour of the cellular type (cytoma) occasionally originates. Probably what happens is that some neuroblasts have not undergone development into ganglionic cells, but have remained latent for a time and have then taken on active growth ; metastases composed only of ganglionic cells, however, have been occasionally reported. Sometimes more primitive cells (sympathoblasts and sympathogonia) may be present in the tumour, and these remain latent for a time and then take on active growth causing metastases. In fact all types of tumours from those composed of mature ganglion cells to those composed of sympathogonia—the least differentiated type of sympathetic nerve cell—are met with. The degree of malignancy varies with the stage of differentiation of the tumour cells.

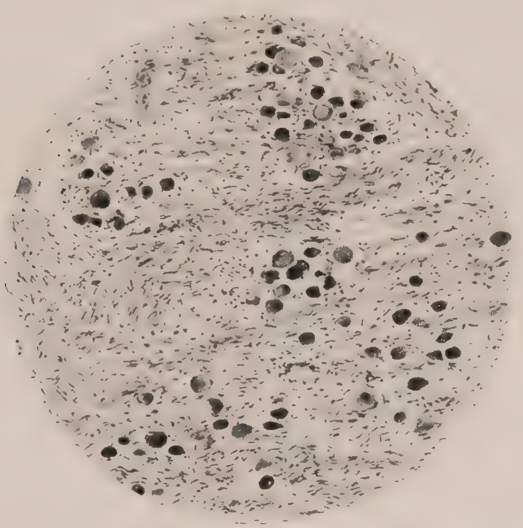

Fig. 132.—Section of Ganglio-neuroma, showing numerous Ganglionic Cells irregularly arranged in Fibro-cellular Connective Tissue. (D. F. C.) × 70.

CHAPTER VII

TUMOURS (*continued*)

II. MALIGNANT TUMOURS—CYTOMATA

Malignant tumours present a contrast to the simple growths in the various points mentioned above. The tissue composing them is essentially cellular, and in its arrangement and general characters does not correspond to an adult tissue. They are not encapsulated, are badly defined at the margin, and their cells infiltrate or permeate the surrounding tissues, which appear to be not only atrophied by pressure, but in many cases actively absorbed by the growing cells. They frequently form secondary growths, and this occurs by the transference of the cells of the tumour by way of the lymphatics or blood vessels to other parts, where they settle and proliferate. Each secondary growth is, accordingly, a transplantation of cells from the original. As a rule, the origin of a malignant growth appears to be from a single focus and the proliferating cells destroy the surrounding tissue, there being no evidence that the normal cells around are stimlulated to take part in the malignant proliferation. Malignancy may arise, however, in multiple independent foci, as is not infrequently seen in primary cancer of the liver (p. 617), and also in cancer of the mamma. Further, while the cells of a malignant growth are generally sharply demarcated from those of the surrounding tissues, it may be impossible sometimes to say exactly where the margin of the growth is. This is especially so in the case of epithelioma (p. 242), where there may be a gradual transition between the cells of the tumour and the adjacent epithelium. Whether this means that the adjacent cells are being stimulated to malignant proliferation by the tumour cells or whether the change in them occurs because they have been exposed to the same irritation, is a difficult question to answer and one on which difference of opinion exists. It is, however, a very important one in connection with the properties of malignant cells.

The cells in malignant growths tend to lose their distinctive characters, or to become de-differentiated. A carcinoma, for example, may consist of irregular masses of rounded or polyhedral cells, which fill the tissue spaces, and have little or no resemblance to the epithelium from which they were derived. To this loss of distinctive character associated with proliferative activity, the term *anaplasia* was applied by Hansemann. It is merely an example of the general rule that the vegetative and functional activities of cells are present in inverse proportion to one another, and that the loss of functional activity is associated with loss of the special histological characters. Whilst the energy of the tumour cells is mainly expended in proliferation, there may, however, be some evidence of functional activity in malignant growths. The most striking example of this is the formation of melanin in melanomata (p. 248). Also bile may be formed by a liver-cell tumour, and colloid by a thyroid carcinoma; and the formation of a cartilage or osteoid matrix in sarcomata is another example of the same occurrence. The cells, both in sarcomata and carcinomata, often become of large size and irregular form, and show great variations in the nuclear structure. Thus a cell may contain several nuclei of unequal size, or a large nucleus of convoluted or lobulated type; such cells are spoken of as *aberrant forms* (Fig. 133). There is also aberration in the types of nuclear division. For example, the chromatin may be unequally divided, one nucleus being hyperchromatic and the other hypochromatic. Multiple mitotic figures also occur, and these represent a process of division into several cells; here too there may be unequal division of the chromatin. Various degenerations, fatty, mucoid, etc., are common in malignant growths; and, especially in the more rapidly growing forms, extensive necrosis often occurs. Hæmorrhages also are frequent, especially in sarcomata, where they are often associated with necrosis. Malignant growths which involve the skin or mucous membrane, frequently undergo ulceration and then become invaded by organisms; the effects of absorption of bacterial products then become apparent. Some facts with regard to the metabolism of malignant growths have already been given (p. 206).

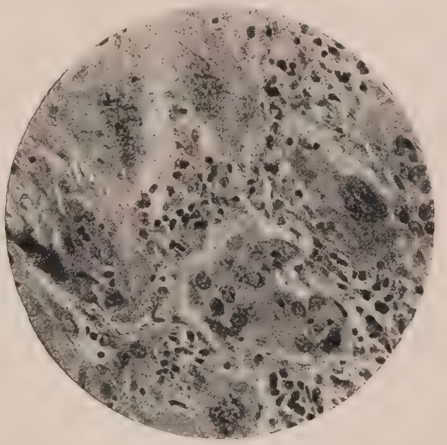

FIG. 133.—Section of Carcinoma of Uterus, showing aberrant Types of Growth of the Cells. × 250.

Varieties of Cytomata. Whilst sarcoma and carcinoma, which originate from connective tissue cells and epithelial cells respectively, form the two main types of malignant tumours, there are others which do not belong to either class. Formerly, cellular tumours which were not clearly of epithelial origin were usually placed amongst the sarcomata ; but there are, of course, cells which are neither of epithelial nor of connective tissue origin, and from these also tumours may spring. It is the case that certain types of growth have not yet been properly differentiated, but we may say that malignant growths may arise also from *endothelial cells*, from *cells of the leucocyte class*, and also from *embryonic cells* of specialised type, e.g. neuroblasts. And lastly, there is a type of growth which takes origin from *multipoten embryonic cells*, that is, cells which are not yet fully differentiated and which have the capacity of forming more than one type of tissue. This variety, which is suitably called *blastocytoma*, will be considered along with the mixed tumours.

SARCOMATA—CONNECTIVE TISSUE CYTOMATA

General Characters. The term sarcoma is applied to a malignant tumour or cytoma of connective tissue origin, and the varieties correspond with the different kinds of connective tissue — ordinary fibrous tissue, bone, cartilage, pigmented tissue, etc. The activity of the cells is mainly proliferative, the tumour remains of cellular character, and, although a certain amount of matrix is formed, this is imperfect and occurs only at places —the tumour as a whole never becomes transformed into adult tissue. Sarcomata often form large masses, usually of somewhat soft consistence, and are frequently the seat of hæmorrhage and necrosis (Fig. 134). Along with the growth of the cells there is an extensive new formation of blood vessels and these are of primitive type, and tend to remain so. Thus between the cells, there are to be seen numerous capillaries and larger channels composed of a single layer of endothelium, supported by the cells of the tumour, while round the larger channels there is usually some fibrous tissue. Owing to the character and large number of the blood vessels, two results follow—on the one hand, the cells of the tumour readily break through the walls and thus *metastases* may follow, and on the other hand, *hæmorrhages* are frequent. The margin of a sarcoma shows a diffuse infiltration of the surrounding tissues with the cells of the growth, and the various tissues are

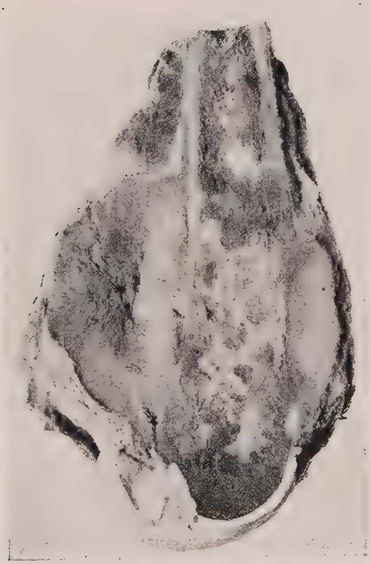

FIG. 134.—Periosteal Sarcoma of lower end of Femur, showing abundant superficial Growth and also Destruction of the Bone.

destroyed and absorbed as the growth advances. Spread by the lymphatic vessels is comparatively rare, except in the case of the melanotic variety and the 'lympho-sarcomata.'

Varieties of Sarcomata

The ordinary sarcomata or desmocytomata take origin from fibrous connective tissue, most frequently in connection with fasciæ, intermuscular septa, subcutaneous tissue and periosteum; but they may occur also in any of the internal organs. The cells composing them vary in form and size in different examples, and there is a varying amount of fine fibrils as matrix between them. Thus *large round-cell*, *small round-cell*, *large spindle-cell* and *small spindle-cell* types are usually distinguished (Figs. 135, 136). In others again, the cells show a great diversity in size and shape, and in the configuration of the nuclei, those in the large cells being multiple or convoluted in form—*mixed-cell* sarcomata, with aberrant types of cells (Fig. 137). All these varieties show the same general features. Although round-cell varieties of sarcoma are usually spoken of, we are doubtful if they really originate from fibrocytes. If this were so, one would expect to find some transitions to the fibroblastic type, yet all the cells may be spherical in form. We believe that most at least of these round-cell growths arise from other types of cells. Many are derived from cells of the leucocyte class, such are chloroma and myeloma; and in some cases from undifferentiated embryonic cells. The neuroblastoma (p. 255), for example, was formerly included

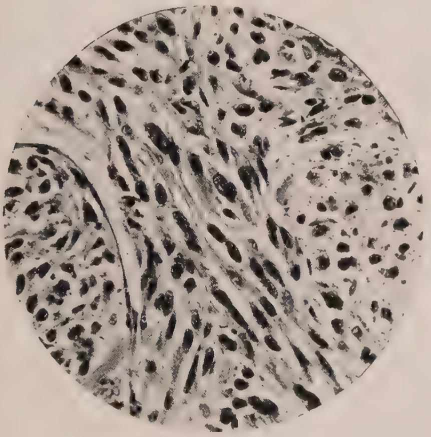

FIG. 135.—Spindle-cell Sarcoma. × 250.

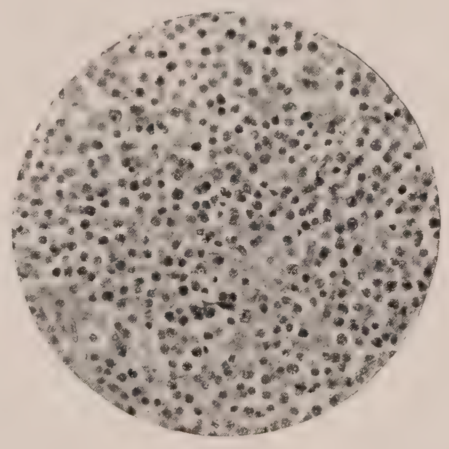

FIG. 136.—Small Round-cell Sarcoma. × 250.

in the sarcomata. Between the spindle-cell sarcomata and the fibromata, all structural varieties with corresponding degrees of malignancy occur, and the term *fibrosarcoma* is applied when there is a considerable amount of formed fibrous tissue. Such a tumour may recur after removal, and it then tends to have a more cellular character. Spindle-cell sarcomata, especially the large-cell variety, often show myxomatous change, and sometimes this occurs to such a degree that the tumour has the somewhat gelatinous and semi-translucent appearance characteristic of myxomatous tissue; the name *myxosarcoma* is then given. Such a tumour may undergo central softening, so that spaces containing clear mucoid fluid are formed.

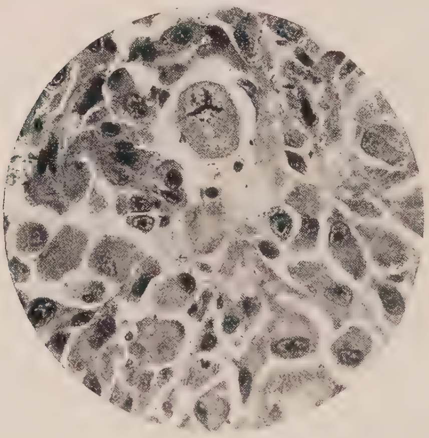

FIG. 137.—Mixed-cell Sarcoma, showing Cells of different shapes, most being of large size.

A multiple mitotic figure is seen in a cell in upper part of field. × 250.

Osteosarcoma and Chondrosarcoma. These are examples of osteogenic sarcomata (p. 838). In the case of the former, distinct trabeculæ of bone are formed at places by the tumour cells, and all stages of transition may be seen between bone and ordinary sarcomatous tissue. A matrix like that of bone may be developed without any calcification following, that is, an osteoid matrix; hence the term *osteoid sarcoma* is applied to this variety. Chondrosarcoma, which is commonest in connection with the long bones, shows in a corresponding way transitional stages between ordinary sarcoma cells and hyaline cartilage, but in the latter the cells are numerous and the matrix is imperfectly formed (Fig. 138). Both osteosarcoma and chondrosarcoma possess a high degree of malignancy. Whilst

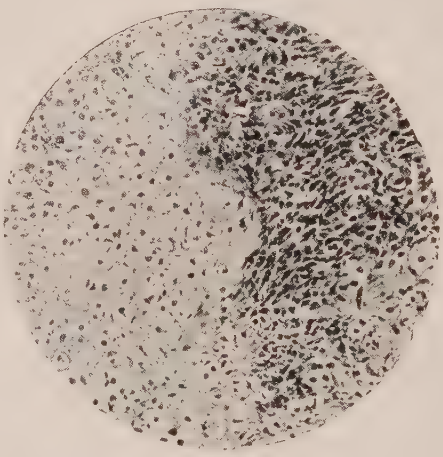

FIG. 138.—Chondrosarcoma, showing imperfectly formed Cartilage with transition to Cellular Tissue. × 100.

these two types of growth ordinarily occur in connection with the skeleton, the formation of bone and cartilage by a process of metaplasia may be met with in sarcomata of the soft tissues; for example, a chondrosarcoma occasionally occurs in the uterus. We may also mention that Russell found bone and cartilage present in sarcomata produced in rats by the subcutaneous injection of tar.

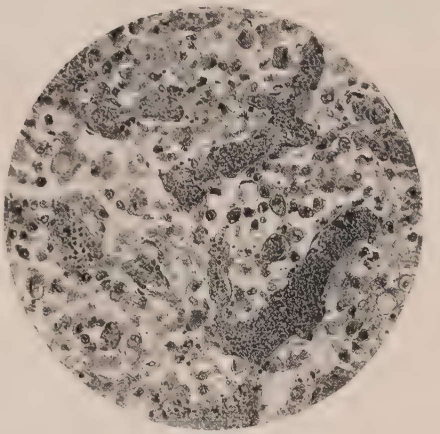

FIG. 139.—Angiosarcoma, showing numerous thin-walled Vessels with Cellular Tissue between. × 150.

Angiosarcoma. In some sarcomata the blood vessels present special features, as regards either (*a*) their size or (*b*) their mode of growth and relation to the cells of the tumour. Sometimes there is a remarkable formation of wide vessels in sarcoma and then the term *angiosarcoma* is often applied, although *angiomatous sarcoma* would be preferable (Fig. 139). Such tumours are extremely vascular and hæmorrhage is of common occurrence. Experiments on the transplantation of tumours show that this feature may be reproduced in a fresh animal; and accordingly it must be regarded as in some way an effect of the cells upon the vessels, since the latter are supplied by the tissues of the new host. There are also rare tumours in which the cells can be seen to take origin from the vascular endothelium. Such a tumour is really composed of endothelial cells derived from the blood vessels, and is thus an endothelioma—an *angio-endothelioma* or *hæmendothelioma.* A rare form of sarcoma is one in which some of the cells are seen to be forming fat—*liposarcoma.* '*Melanotic sarcoma*' is described on p. 248, *lympho-sarcoma* on p. 254, and the cellular tumours of the neuroglia, *gliosarcoma* on p. 790.

Myeloid Sarcoma. This tumour, also known as *osteoclastoma,* occurs chiefly in connection with bones, especially the extremities of the long bones. It often causes marked absorption and expansion of the end of the bone, so that there may be left a mere shell on the surface, which gives a crackling sensation when handled. The tumour is usually very vascular and hæmorrhage often occurs into its substance (Fig. 140); while the central parts of the growth may be softened and destroyed and their place taken by a brownish fluid, a sort of false cyst being formed (Fig. 527). On microscopic examination, the tumour is composed essentially of two types of cells, viz. large multi-nucleated cells like osteoclasts, and small cells usually of a spindle shape (Fig. 141). Such tumours grow somewhat slowly and very rarely lead to metastases, and they are regarded by some as really non-malignant or only locally malignant. Nevertheless, secondary growths are occasionally produced by myeloid tumours of the long bones. Some writers consider that the giant-cells do not really form part of the tumour, but are osteoclasts which have been stimulated to activity and are concerned in the absorption of the bone. Giant-cells have, however, been observed in secondary growths. A myeloid tumour is not uncommon in connection with the lower jaw, forming a type of *epulis*; it very rarely recurs after removal and may be regarded as almost a simple growth. The term 'myeloma' (p. 519) has in recent years been applied by some writers to myeloid sarcoma. 'Myeloma' has, however, been used for a considerable time to signify a round-cell tumour growing from the cells of the bone-marrow, and should be applied only with this significance.

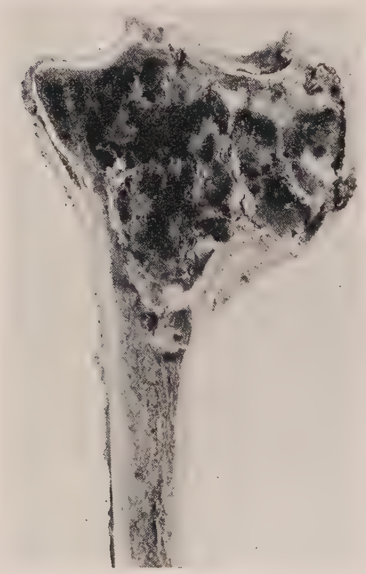

Fig. 140.—Section of Myeloid Sarcoma of upper end of Tibia with much Hæmorrhage into its Substance.

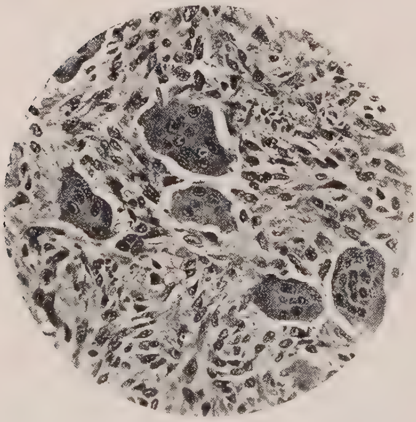

Fig. 141.—Myeloid Sarcoma, showing multi-nucleated Giant-cells embedded in Spindle-cell Tissue. × 200.

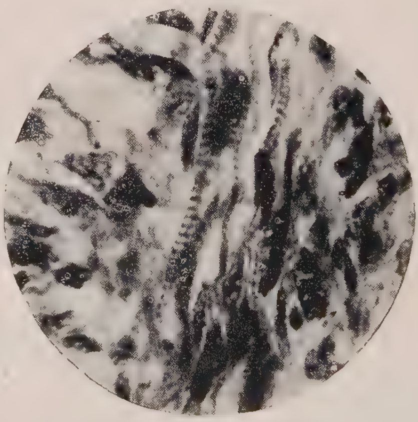

Fig. 142.—Rhabdo-myosarcoma, showing Spindle Cells, some of which show distinct Striation. (J. S. D.) × 400.

The so-called 'myeloma of tendon sheaths' is quite a distinct condition. It is described later (p. 842).

Myosarcoma. Occasionally a malignant growth develops in connection with a leiomyoma, and its cells may be traced to take origin from the muscle cells. Such a growth is accordingly called a *myosarcoma* or leiomyosarcoma. And further, as has been stated above, a rhabdomyoma not infrequently has malignant properties, and then the term *rhabdo-myosarcoma* may be applied (Fig. 142).

CARCINOMATA—EPITHELIAL CYTOMATA

Under the term carcinoma we include all the malignant growths taking origin from and composed of epithelial cells, whilst special terms are applied to varieties, such as squamous epithelioma, rodent ulcer, chorion-epithelioma, etc.

General Characters. The two essential features are the continued proliferation of the epithelial cells and the invasion of the tissue spaces by them, the latter phenomenon, of course, implying that the cells have broken through their normal bounds, basement membranes, etc., and have come to produce an injection of the tissue spaces. The preliminary multiplication, before the break-through takes place, is not often seen, but in 'intraduct carcinoma' of the breast, cells presenting all the appearances of cancer cells may be seen still contained within the ducts. In such a case the change characteristic of malignant neoplasia has no doubt begun and, it may be added, the malignant proliferation within the ducts may go on for some time before the actual invasion of the tissues outside takes place.

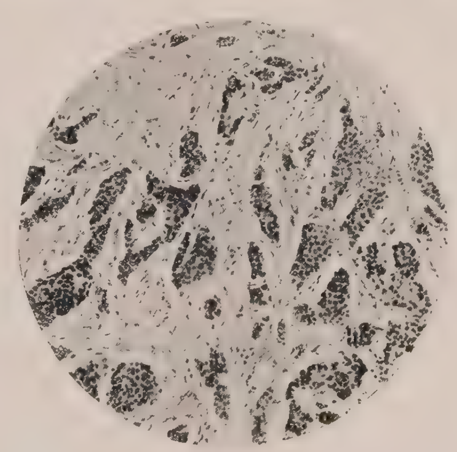

FIG. 143.—Scirrhous Carcinoma of Breast, showing Cancer Cells in tissue Spaces with dense Stroma between. × 100.

As the cells pervade the tissue spaces and increase in number, they come to form strands or masses with irregular outline (Figs. 143, 144). At the same time their presence exerts an irritative effect on the intervening connective tissue; proliferation takes place and thus the stroma of the growth results. This is essentially a secondary matter, and the stroma should not be regarded as really a part of the tumour. For example, when a cancer with very dense stroma gives rise to a secondary focus, say in a lymphatic gland, there is no stroma when the cells first arrive in the gland and any stroma afterwards formed may be scanty. So also, when carcinoma is inoculated from one animal to another of the same species, it is only the epithelial cells which survive and grow, the stroma in the new growth being supplied in a reactive manner by the tissues of the inoculated (normal) animal. The proportion of cells to stroma varies very much, and to this fact the varieties in the naked-eye characters are chiefly due. Thus the consistence of the growth depends upon the rate of multiplication of the cells on the one hand, and upon the amount of irritative reaction of the connective tissue on the other.

In addition to stroma formation, lymphocytic accumulation around cancer cells is often a well-marked feature, and a number of facts point to its being an important defensive reaction; it is certainly related to restricted growth. Most of the facts, however, with regard to the phenomena have been established by experimental work. Murphy found that a general lymphocytosis is related to immunity and also that a local lymphocytosis has an inhibitory action on carcinoma when it is transplanted at the site of the lymphocytosis. He found, further, that in such cases destruction of the lymphocytes by X-rays was followed by a disappearance of the resistance. It has also been shown that the production of a lymphocytopenia by damage to the lymphoid tissues by means of radiation or benzol, lowers the resistance to transplanted growths. A lowering of the resistance has also been produced by blockade of the reticulo-endothelial system by means of dyes (Ludford), apparently by interfering with the supply of monocytes and lymphocytes. In view of all the facts one must consider that the lymphocytic reaction represents an important means of defence, though there is no evidence of direct action of lymphocytes on cancer cells. On the other hand, it is difficult to reconcile this view with the fact that cancer flourishes so well in lymphoid tissue and is so rare in the splenic pulp. It must also be borne in mind that lymphocytic infiltration is common in noncancerous states around epithelium in an abnormal condition or undergoing atrophy; this is well seen in the case of the thyroid gland.

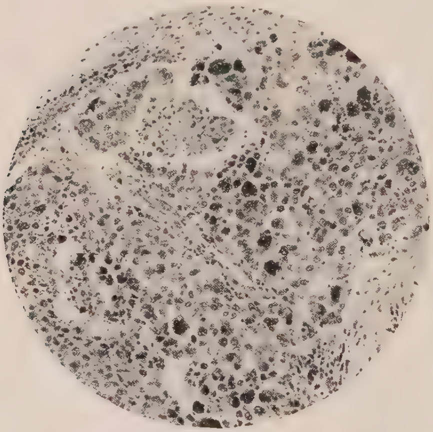

Fig. 144.—Encephaloid Carcinoma of Breast, showing two large alveolar Spaces filled with Cancer Cells of aberrant type, with little Stroma between. × 100.

The term *scirrhous* or hard is applied when the growth is dense and there is little or no increase in bulk, and the term *encephaloid* is applied to a soft, bulky cancer, often resembling a sarcoma in appearance. In both varieties, owing to the infiltration, the margin of the growth is ill-defined, and, on microscopic examination, collections of cancer cells can be seen scattered in the tissues beyond.

The thickening and shrinking of the stroma may sometimes lead to an actual diminution in the size of the part, as is common in cancer of the breast: and to such contraction in slowly growing cancers many of the obstructive results of cancer growth are due. The terms mentioned, however, are merely to be used in a descriptive sense and not as indicating distinct varieties. It is to be noted that a scirrhous carcinoma may give rise to secondary growths in which stroma is relatively scanty, and which are comparatively of large size. This action of cancer cells, in leading to proliferation of the connective tissue, varies also according to the nature of the epithelium from which the growth has originated. In the case of growths from squamous epithelium, for example, there is usually a loose stroma in the meshes of which are a large number of lymphocytes; whereas a growth from glandular epithelium, notably that of the mamma, often gives rise to a dense indurated stroma. It may be added, however, that in the hard cancers the infiltrative property is as pronounced a feature as in the soft rapidly-growing varieties; in fact, widespread metastases are often present when the primary growth is small and indurated.

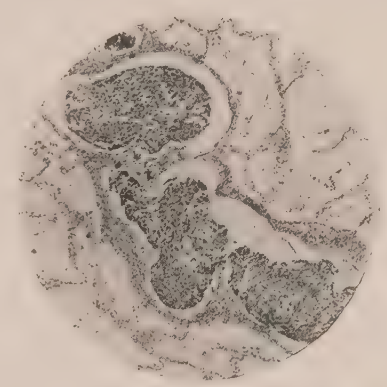

Fig. 145.—Secondary Cancerous Invasion of Lung.

The masses of cancer cells are seen distending the lymphatic spaces. × 45.

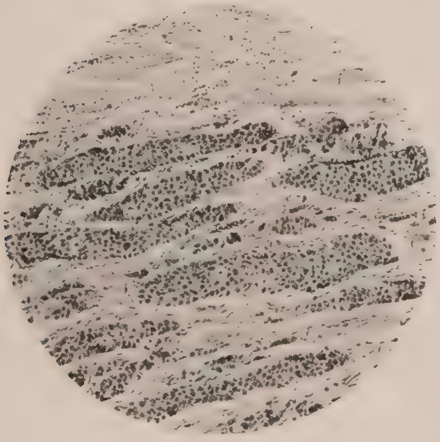

Fig. 146.—Cancerous Invasion of Muscle.

The muscle fibres are invaded by cancer cells which form elongated masses replacing the sarcous substance. × 60.

Spread by the Lymphatics. This is one of the most characteristic features of carcinoma and is of prime importance from the surgical point of view. Cancer cells may enter the lymphatic vessels and be carried to the glands at an early period, and they may also become arrested in their course and form small foci of growth which obstruct the lymphatics. In this way nodules are formed along the lines of the lymphatics, or the latter may be practically injected with proliferating cancer cells (Figs. 145, 147). A very important point is that lymphatic extension may take place in a direction contrary to normal lymph flow, and this occurs especially as a sequel to the lymphatic obstruction. Such is well exemplified in the case of cancer of the mamma, where the lymphatic spread may be extensive in practically any direction. So also in cancer of the stomach, the supra-clavicular glands on the one hand and the inguinal glands on the other, may be the seat of secondary extension. It is important to note that many of the secondary foci in the region of a carcinoma are of quite microscopic size, and tissues may be unchanged in appearance though extensively involved It is accordingly quite impossible to judge as to absence of secondary invasion by naked-eye examination alone. The presence of these minute collections of cancer cells explains the so-called *recurrence* of cancer after surgical removal. Recurrence, in fact, is not to be regarded as a fresh start or recrudescence of the disease, but simply the result of growth from cells which have been left behind in the surrounding tissues. Further, such cells may remain in a comparatively dormant state for a considerable period of time, so that occasionally even several years may elapse before a recognisable growth appears.

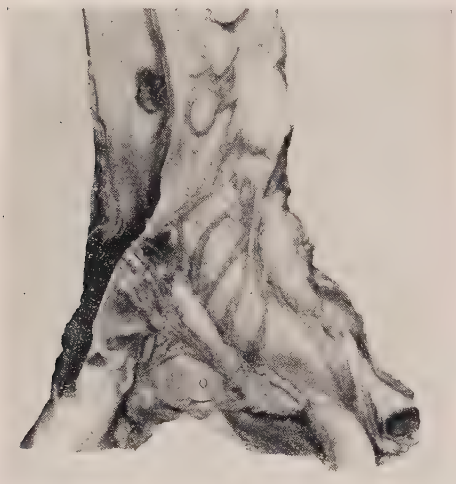

Fig. 147.—Cancerous Invasion of Lymphatic Vessels and Glands over lower end of Aorta.

The lymphatics are seen as distinct cords.

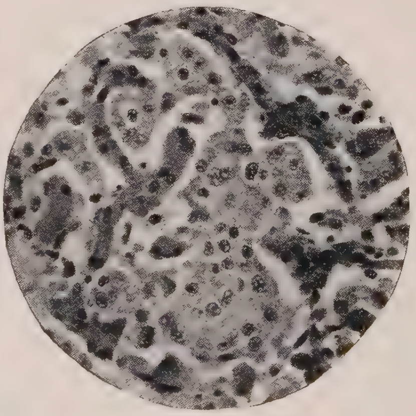

Fig. 148.—Secondary Cancerous Invasion of Liver.

Note masses of cancer cells in the sinusoids between the liver cells, without any formation of stroma. (G. McC.) × about 200.

Carcinoma may spread also by the blood stream and sometimes very widespread metastases are met with. In cases of carcinoma of the stomach and bowel, numerous secondary nodules may be produced in the liver in this way (Fig. 148), as well as by lymphatic extension, and similarly in the lungs when the cells have gained access to the systemic venous circulation.

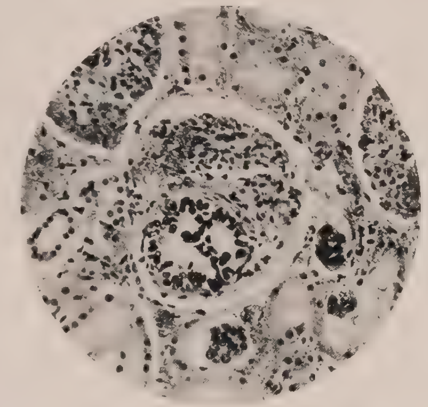

Fig. 149.—Section of Kidney showing Embolus of Cancer Cells in Glomerulus and smaller Emboli in Inter-tubular Capillaries. (D. F. C.) × 150.

In Fig. 149 actual embolism in a Malpighian body in the kidney is shown. Not infrequently, numerous secondary growths are present throughout the osseous system even without visible growths in the lungs, and thus the question arises as to the mode of entry of the cancer cells into the systemic circulation. Another fact to be considered in this connection is that extensive metastases in the bones are met with especially when the primary growth occurs in certain sites, notably mamma, prostate or thyroid (Fig. 151). It was shown first by Schmidt that in a considerable proportion of cases, where there are no visible secondary growths in the lungs, the presence of emboli of cancer cells in minute branches of the

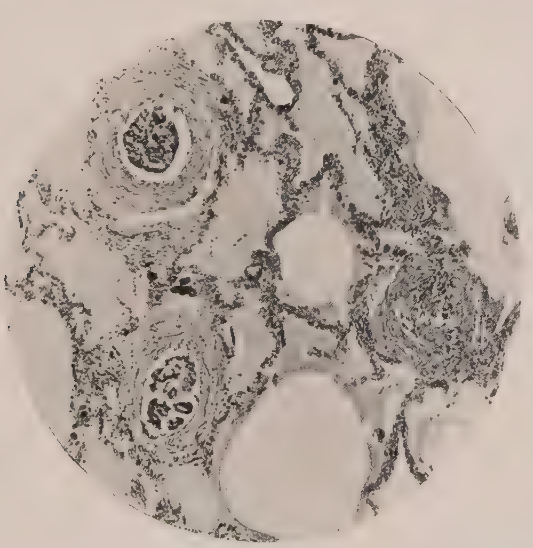

Fig. 150.—Section of Lung from a case of Prostatic Cancer, showing two Pulmonary Arterioles containing Cancer Cells.

A third arteriole (to the right) has become obliterated, but at another level it also contained cancer cells. (Dr. A. A. Charteris.) × 60.

pulmonary arteries can be demonstrated on microscopic examination. The cancer cells often lead to a reaction on the part of the vessel wall resulting in their encapsulation, and subsequent atrophy and disappearance. On the other hand, they may grow onwards into the capillaries and venules and thus lead to dissemination in the general circulation. I can confirm this observation, and Fig. 150 shows a section of lung with emboli of cancer cells from a case of prostatic cancer where no growth could be seen in the lungs on naked-eye examination. It is a possibility that occasionally cancer cells may slip through the pulmonary capillaries, but there appears to be little doubt that Schmidt's explanation holds in the majority of cases. It may be noted that he found such emboli in the lungs in many cases of cancer originating in various sites—stomach, rectum, ovaries, etc., without there being evidence of further metastases by the blood stream, these being prevented by the healing-in process referred to.

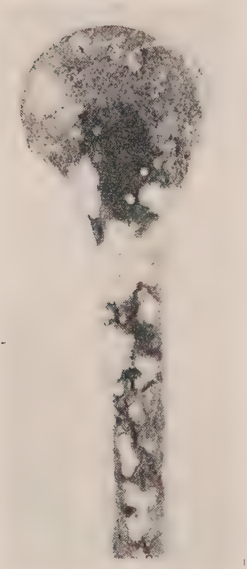
FIG. 151.—Multiple Cancerous Nodules in Humerus in a case of Cancer of the Breast.

But while we can understand the mode of transference to the lungs and beyond them, the *distribution* of the subsequent metastases cannot be satisfactorily explained. It cannot be doubted that emboli must be arrested often in the capillaries of the skin, muscles, various organs, etc., and it seems impossible to escape the conclusion that they often undergo destruction. In fact, the observations on the lungs referred to show that this actually occurs.

With regard to the question why some tissues are frequently the site of blood-borne cancer and others are exempt, we can say nothing definite. We can speak of varying degrees of resistance of different tissues, for such evidently exist; but we know nothing of the nature of the resistance and it would be idle to speculate. In cases of bone metastases, the tumour cells appear to settle first in the bone-marrow and this tissue seems to afford a specially favourable nidus for their growth. In this respect there is a contrast to the splenic tissue, which is relatively immune, although, in view of its function of separating abnormal elements from the blood stream, one would expect metastases to be frequent in the spleen. I have long had the idea that tumour cells may be destroyed in the spleen, and I may mention that Cappell has found cancer cells in the splenic pulp in several cases when there was no change visible to the naked eye. The cells, which were chiefly situated around the Malpighian bodies, appeared to be in an inactive and partly degenerated condition and had been unable to lead to the formation of distinct nodules. A similar low incidence in the occurrence of metastases in the spleen has been observed in the case of tumours experimentally produced or transmitted in the lower animals. These findings are of interest in connection with what has been definitely established in the case of the lungs.

Intra-epithelial Spread. When a carcinoma has originated in a glandular tissue the cancer cells may sometimes be seen growing within relatively normal epithelium, from the cells of which they are readily distinguished. This is well seen in carcinoma within the ducts of the mammary gland before it has broken through into the surrounding tissue. But the most striking examples of intra-epithelial growth are seen in the case of the epidermis and they are met with in the following three conditions. (*a*) A primary carcinoma of the epidermis may be restricted in its growth to the epidermis and may spread widely without passing deeply. Such a growth, however, is often of multicentric origin as in Bowen's disease. Infiltrative growth of the subjacent tissues may appear later and may be of the nature either of ordinary squamous epithelioma or basal-cell carcinoma. (*b*) Carcinoma within ducts, notably of the breast, may reach the epidermis and its cells then wander in it, producing a variety of appearances (see Paget's disease of the nipple, p. 911). (*c*) There may be direct spread of carcinoma in the underlying tissues to the epidermis, and the cells may then spread in the latter, as in the previous case. In all these examples the growth of the carcinoma seems to be of restricted nature in the epidermis, and occurs especially in the deeper parts.

Varieties of Carcinomata

Theoretically, there are as many types of carcinoma as there are of epithelium in the body. And although it is the case that carcinomata most frequently take origin from the covering epithelium of skin and mucous membranes, they may arise also from highly specialised epithelium, e.g. of the liver, adrenals, etc. The term ‘ cancer ’ or ‘ carcinoma ’ without qualification accordingly means any malignant growth of epithelial origin. Certain terms are, however, commonly used to indicate varieties with special features and these may be conveniently referred to.

Glandular Carcinoma. Under this heading it is convenient to include, not only the growths which take origin from the acini of glands, but also those which are derived from columnar or cubical epithelium, covering mucous surfaces or lining ducts. The two kinds of epithelium have, of course, different types of function, but the growths originating from both have pretty much the same characters.

After the cells of a carcinoma have invaded the connective tissue spaces, their arrangement varies in different cases. The most atypical arrangement is seen when the cells are somewhat rounded or polyhedral in form, and adhere together to form masses or conglomerates of various sizes. This is often called *spheroidal-cell carcinoma* or *alveolar carcinoma*, the cells showing no attempt to reproduce a gland-like arrangement (Fig. 152). In other cases, however, the cells are more cubical or columnar in type, and tend to form a more or less complete lining to the alveoli in which they lie, and thus to reproduce, though imperfectly, glandular structure. The lining of the alveoli may be fairly regular at places, but usually there is evidence of the excessive proliferation, and the epithelial layer may be irregularly folded or the cells heaped up in masses (Fig. 153). Tumours of this type are usually called *adenocarcinomata*, but the term has merely a histological significance, indicating that the cells tend to arrange themselves in a layer as in a tubular gland, and in the same growth all transitions to an irregular arrangement of cells may be seen. Adenocarcinomata correspond in their naked-eye appearances and general characters

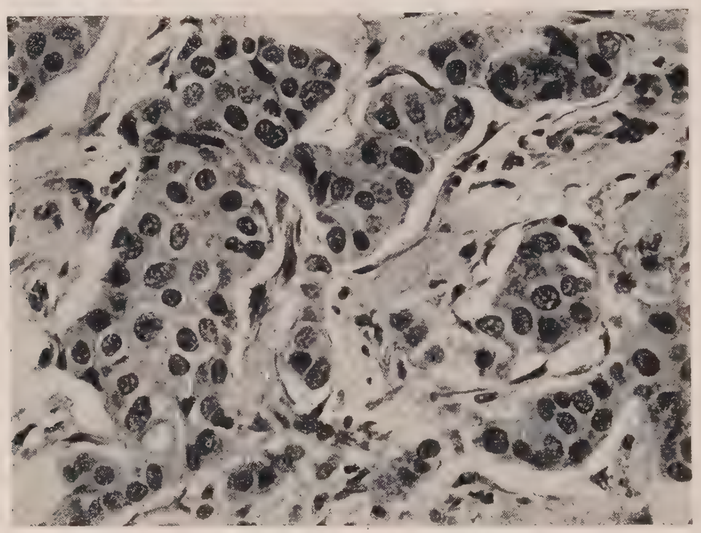

Fig. 152.—Spheroidal cell carcinoma of mamma infiltrating tissue spaces.
Note anaplastic character of cells. × 300.

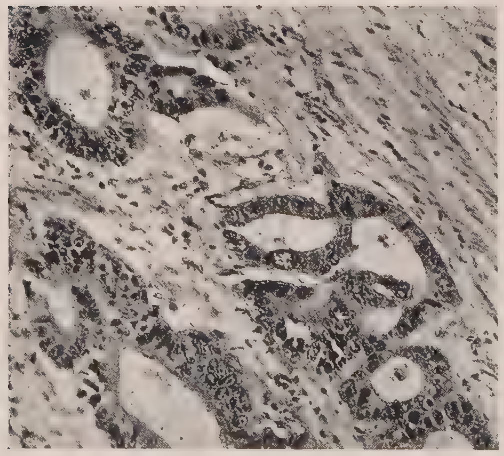

Fig. 153.—Adenocarcinoma of Bowel invading the Muscular Coat.
Note the arrangement of the cells, acinus-like but with evidence of excessive proliferation at places. × 200.

with other carcinomata. Sometimes again, there may be irregular papilliform processes formed in places by the cancer cells, whilst elsewhere the cells may be arranged irregularly; this is seen, for example, in some lung and thyroid carcinomata. In cases of carcinoma growing from liver cells we have another example of an attempt to reproduce the original structure (Fig. 154). The cells are arranged in columns or trabeculæ, and the general structure may mimic liver tissue, though the cells are altered in type. Gland-like, papilliform and trabecular forms of growth are thus met with in these carcinomata. The terms *scirrhous* and *encephaloid* are merely descriptive and, as already explained, are applied to any form of glandular cancer.

The energy of the cancer cells is essentially directed to proliferation, but when this becomes less active, evidences of attempt to perform their special functional activities are also seen. For example, in cancers of the liver and thyroid there may be formation of bile and colloid material respectively. Cancers on the whole have relatively little vascularity, hence the ordinary yellowish-white appearance, but not infrequently there is a considerable amount of formation of new vessels at the periphery. In some varieties, the cancer cells induce an extensive development of new vessels, seen both in the primary and secondary growths, and wide vascular channels may be formed, the variety known as *telangiectatic* cancer then resulting.

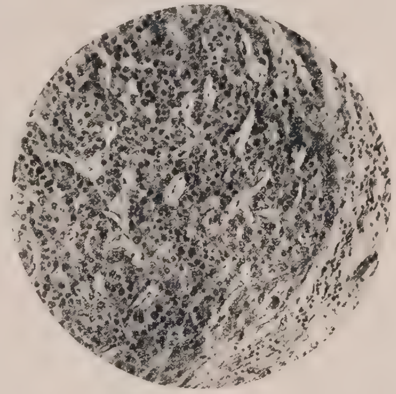

FIG. 154.—Portion of Carcinoma arising from Liver Cells, showing trabecular arrangement. × 100.

Colloid carcinoma or, more properly, **mucoid carcinoma,** has certain characteristic naked-eye and microscopic features. It is essentially an alveolar carcinoma, in which the cells form much mucin, and then undergo mucoid change and become fused with the mucoid material (Fig. 155). Thus many alveoli may be occupied merely by mucoid material, no cells being present. Such tumours are commonest in situations where mucin-forming cells abound, notably in the large intestine, biliary passages, stomach, etc., and we have little doubt that they originate from such cells. The tissue of the tumour has a somewhat characteristic semi-translucent appearance, and in places it may be softened and glue-like. One striking feature is the large masses of tissue which are produced in some instances, and this applies both to the primary and secondary growths. We have seen the wall of the stomach two or three inches in thickness owing to a mucoid cancer, whilst the lumen was very much reduced. Secondary growths are not uncommon in the omentum and in the peritoneum, and may sometimes form colossal masses. Nevertheless, we believe that secondary growths do not usually occur at so early a stage in mucoid cancers as in the ordinary forms, and this may be because the mucoid material blocks the lymphatics and prevents the spread of the cells. In some cancers the stroma rapidly undergoes myxomatous or gelatinous change, as the tumour spreads; the term *carcinoma myxomatodes* is then applied (Fig. 156).

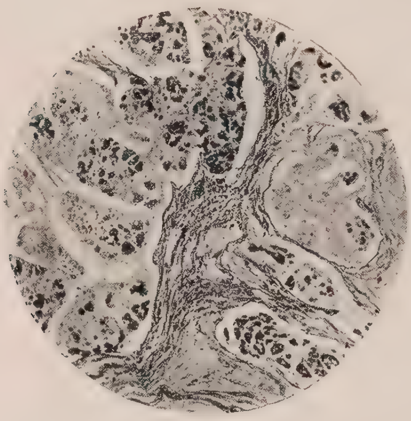

Fig. 155.—Colloid or Mucoid Cancer.

The alveoli contain mucoid material and degenerating cancer cells. × 65.

Squamous Epithelioma. The term is applied to malignant growths derived from the stratified squamous epithelium of the skin or of a mucous membrane. Occasionally they take origin from an epithelium which has undergone metaplasia into the squamous type, *e.g.* in gall-bladder, renal pelvis, etc.; they may also arise from cellular inclusions of congenital origin, *e.g.* from branchial clefts, dermoid cysts, etc. Squamous epithelioma is sometimes known as *acanthoma*, which means a prickle-cell tumour.

Their origin is often related to chronic irritation, and the first change which occurs is a thickening of the epithelial layers and down-growth of the interpapillary processes. Such changes are, however, common at the margin of any chronic ulcer, and it is often difficult to say whether or not a malignant growth has started. After a time, however, the epithelium penetrates deeply

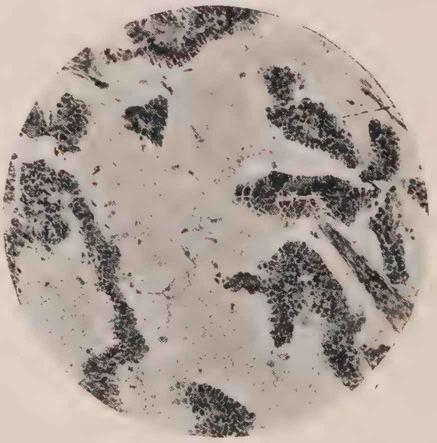

Fig. 156.—Carcinoma Myxomatodes, showing irregular masses of Cancer Cells separated by abundant myxomatous Stroma. × 80.

as branching processes which invade the tissue spaces and destroy intervening structures, such as muscle (Fig. 157). For a time, the cells form a continuous mass and the shape of the growth may be compared to an inverted cauliflower. Later, however, the cells become detached and wander in the tissue spaces and into the lymphatics ; they are thus carried to lymphatic glands, where they produce secondary growths. Metastases may occur in internal organs, but are rarer than in the case of glandular carcinoma. If the relation of the original epithelium be studied, it will be seen that the deepest layer of cells passes on to the outer aspect of the cell masses of the tumour. The central parts of these masses thus correspond with the more superficial layers of the epithelium ; and accordingly, the cells towards the centre become somewhat flattened and concentrically arranged, and ultimately undergo a sort of hyaline or horny change. Such concentric structures, which are of common occurrence in epitheliomata, are usually known as *cell-nests* or epithelial pearls (Fig. 158). The number and character of the cell-nests depend in part upon the nature of the original epithelium. Thus an epithelioma of the skin usually contains many cell-nests and these generally show a keratinised centre. In an epithelioma of the tongue they are fairly prominent, as a rule, but the centres show rather a hyaline change, and, again, in certain situations, e.g. in the larynx and cervix uteri, the formation of cell-nests may be almost absent. This is, however, not the whole explanation, as considerable variety of structure is met with in the same situation and in association with varying degrees of malignancy. Sometimes the cells are in thin strands forming practically an injection of the tissue spaces ; occasionally they are spindle-shaped, and it may be difficult to distinguish them from sarcoma cells. The method of ‘grading’ tumours in different groups according to malignancy, introduced in recent years, has been applied especially to epitheliomata ; but it depends mainly on the general principle that the more the growth is dedifferentiated or anaplastic, the more malignant it is and also the more sensitive to radiation.

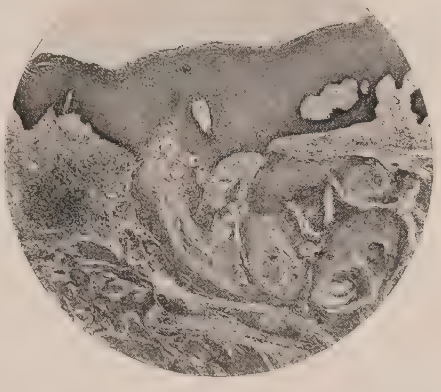

FIG. 157.—Squamous Epithelioma, showing masses of Epithelial Cells extending downwards from surface epithelium and invading the tissues, also formation of Cell-nests. × 30.

The reaction around the infiltrating epithelial cells is somewhat different from that seen in glandular cancers. The connective tissue fibres do not undergo, as a rule, the same degree of thickening, whilst there occurs a very marked infiltration of lymphocytes, so that the stroma often has a cellular appearance. Evidences of phagocytic reaction are not uncommon. Occasionally, the cell-nests may become invaded by polymorpho-nuclear leucocytes, and the central parts may be occupied by large masses of these cells. Then, again, multi-nucleated phagocytes—foreign-body giant-cells—(Fig. 49) may be present at the periphery. There is little evidence, however, that such phagocytic reaction leads to any effective destruction of the tumour.

An epithelioma appears first as an indurated thickening of the skin epithelium or mucous membrane. Its growth is usually slow and its margins are badly defined. Ulceration generally occurs at a somewhat early stage, and then the lesion appears as a progressive ulcer with irregular and indurated floor and margins. Continuous growth and ulceration go on, until ultimately there may be extensive destruction of tissue. Hæmorrhage from erosion of vessels is of common occurrence and occasionally a fatal result is produced by the implication of a large artery. In the case of epitheliomata about the mouth, death is not infrequently caused by passage of discharge from the ulcerating area into the trachea and bronchi, with septic pneumonia as a result.

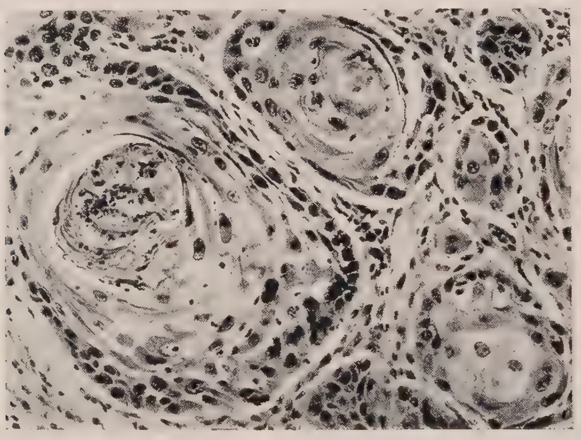

FIG. 158.—Higher-power view of Squamous Epithelioma, showing characteristic Cell-nests. × 180.

A variety of anaplastic epithelioma with distinct characters has recently been differentiated and has been called *lympho-epithelioma.* It occurs in the naso-pharynx, arising from the modified epithelium overlying the lymphoid tissue of the tonsils, etc. The tumour is composed of rounded or polyhedral cells of somewhat indifferent character, though at places they can be clearly recognised as epithelial. The growth of the cells is associated with marked lymphocytic accumulation (Fig. 159). Such tumours, which are not uncommon, infiltrate deeply and sometimes also give rise to metastases in internal organs. In the metastases the associated presence of a large number of lymphocytes is again noteworthy. This type of epithelioma is met with in the earlier years of life as well as later, and an important feature is that it is markedly sensitive to radiation. Another point is that extensive growth in the cervical glands often occurs when the primary tumour is small.

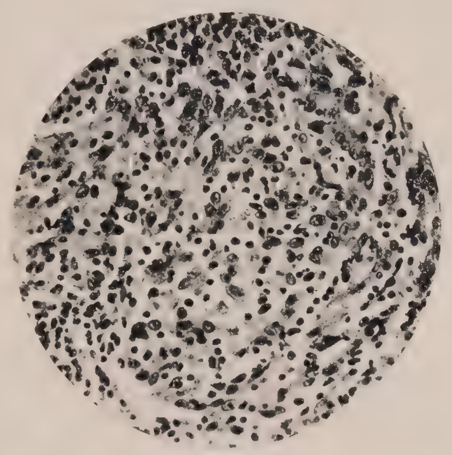
FIG. 159.—Lympho-epithelioma, showing tumour cells in trabecular arrangement, with rich lymphocytic accumulation between. (D. F. C.) × 190.

Rodent Ulcer or Basal Cell Epithelioma. The former term is convenient, as it represents a distinct clinical type of growth, although the histological structure varies in different cases. Its common site is the face, and it often occurs at the junction of skin and mucous membrane, at the margin of the eye or ear, ala nasi, or the lip. It appears first as a somewhat flat nodular thickening, which later undergoes ulceration. Its extension is very slow and is chiefly in a superficial direction, whilst there is little tendency to involve the deep structures until a late stage is reached. The surface may become dry and scabbed over, and there may be appearances, from time to time, suggestive of healing. Nevertheless, the growth is progressive, and ultimately may produce extensive destruction of the superficial tissues. Another point is that the tumour usually remains strictly local. Secondary growths in lymphatic glands have been described, but we have never met with their occurrence. The microscopic structure varies, as we have said. The

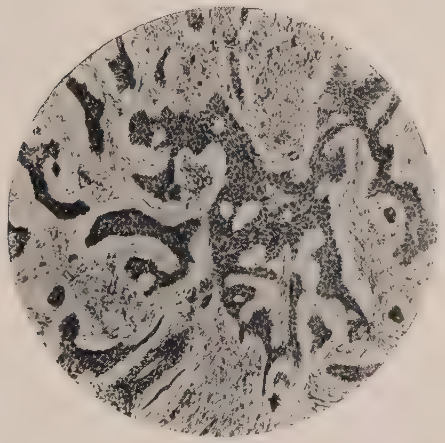
FIG. 160.—Section of Rodent Ulcer, showing masses of small Epithelial Cells filling irregular Alveoli. × 60.

growth is composed usually of rounded or polyhedral cells of somewhat small size, irregularly arranged in alveoli like an ordinary scirrhous cancer (Fig. 160). Not infrequently, the cell masses are drawn out into thin bands in the thickened stroma, there being thus a sort of reticulated appearance, and some of the cells may be spindle-shaped. No cell-nests are present in rodent ulcer as a rule, but intermediate forms between a rodent and epithelioma are met with. Rodent ulcer is believed to take origin from the lowest layer of the surface epithelium, and this seems to us to be usually the case; it is often spoken of as an *epithelioma basicellulare*. The appearance of the cells of the growth often suggests such an origin, and it is not uncommon to find direct continuation between the growth and the rete Malpighii (Fig. 161). Occasionally multiple foci of origin can be seen. Rodent ulcer is much commoner in Australia than in this country. It has been investigated in Sydney by Molesworth, who considers that it is due to ionisation by the ultra-violet component of sunlight, and finds that it is commonest in those with fair or red hair and with a tendency to freckling.

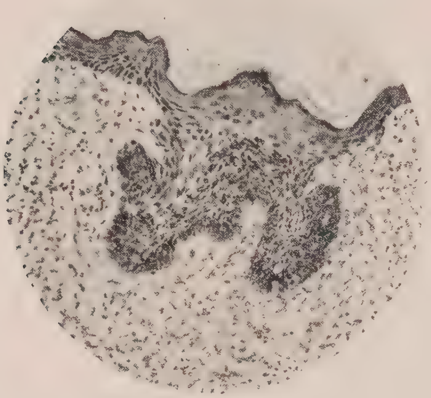

FIG. 161.—Early Rodent Ulcer showing origin from deep part of epidermis. × 125.

In other instances, the cells of a rodent have more of an irregular adenomatous arrangement and the appearance suggests an origin from the sweat glands. In others, again, the cells occur in large areas with blunt processes at the margin (Fig. 162), and here and there in the cell masses there may be a suggestion of an acinus with a lumen. Other features may be present, and a considerable variety of rodents have been

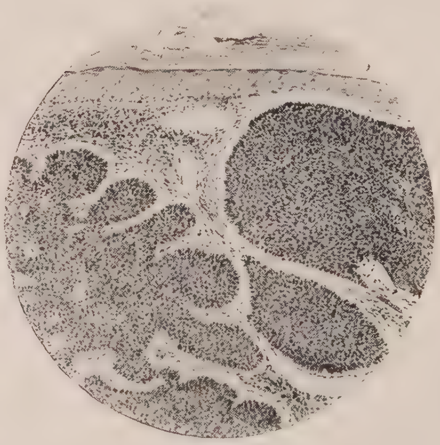

FIG. 162.—Another type of Rodent Ulcer, showing broad masses of cells with suggestion of acinous arrangement.

The surface epithelium is seen above. × 60.

described. It would appear as if tumours, originating from the deep layer of the skin epithelium, or from the sweat glands or hair follicles, might present the general characters of a rodent as above described, and this is quite intelligible in view of the common origin of these structures.

Chorion-Epithelioma. This is an interesting type of growth as it is derived from the cells of the fœtus, which come to invade the maternal tissues. It usually occurs in connection with a mole pregnancy (p. 894) and it may sometimes be clearly seen to take origin from the chorionic epithelium covering the villi. As in the original trophoblast, two distinct types of cells are present, namely, syncytia or plasmodial masses, and the cells of Langhans' layer. The former are of large size and very irregular outline, often possessing long processes which extend amongst the other cells (Fig. 163). They have many nuclei and their protoplasm is finely granular and somewhat eosinophile. The Langhans' cells are of rounded form and possess a single spherical nucleus; their outline is rather badly defined. The growth, which leads to the formation of little or no stroma, is highly malignant, invading the tissues locally and producing metastases in the lungs, liver, and other organs. The cells of the trophoblast have an important function in penetrating the walls of the maternal blood vessels and thus allowing the entrance of the villi, and it is interesting to note that this activity is reproduced in the chorion-epithelioma. The cells of the growth have a marked tendency to infiltrate and soften the walls of the blood vessels, and hence hæmorrhage is of frequent occurrence. As a result, both primary and secondary growths usually present a markedly hæmorrhagic appearance. Tendency to degeneration and necrosis is often an obvious feature, and when these changes are marked the histological characters of a chorion-epithelioma may be distinct only at the margin where it is actively growing. Chorion-epithelioma may originate also from a teratoma, in the male sex as well as in the female.

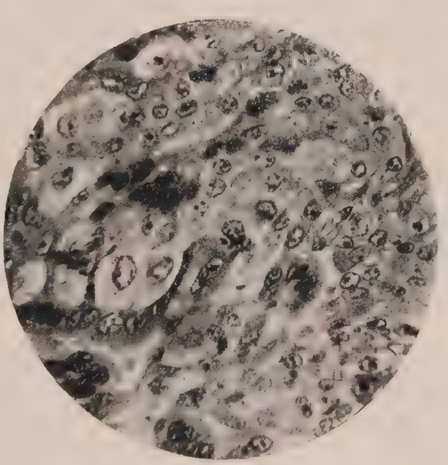

FIG. 163.—Chorion-Epithelioma, showing the large multi-nucleated Syncytia and Langhans' cells. (Prof. J. H. Teacher.) × 250

An interesting fact, established by Teacher, is that sometimes secondary nodules in the lungs undergo a process of involution and healing. The extensive hæmorrhage into a nodule may be followed by necrosis of its substance, and thereafter the nodule may become encapsulated by connective tissue and undergo a certain amount of shrinking. Such an occurrence is of interest as showing that the growth of a malignant nodule may come to an end; but the course of the disease as a whole is not affected.

Malignant Melanoma.

The type cell is here the melanoblast, a cell which has the property of forming melanin. Melanotic growths arise most frequently from the skin, usually from pigmented moles, or from the pigmented coats of the eye; occasionally in the internal organs, e.g. the adrenals and brain. The proliferating cells at first are free from melanin, but this soon appears in their cytoplasm and may accumulate to such an extent as to obscure their structure. Ultimately, many cells break down and much pigment is set free. The free pigment is taken up by histiocytes, the cytoplasm of which becomes crammed with it and the nuclei are obscured; in fact some of the most deeply pigmented cells are these phagocytic cells which have ingested pigment. Such cells, which are called melanophores or melanophages, in their turn may likewise become disintegrated. Proliferation of the tumour cells may go on for some time without pigment appearing, and when there are multiple secondary growths, some may be comparatively pale, whilst others are jet black. Melanomata vary much in the characters of

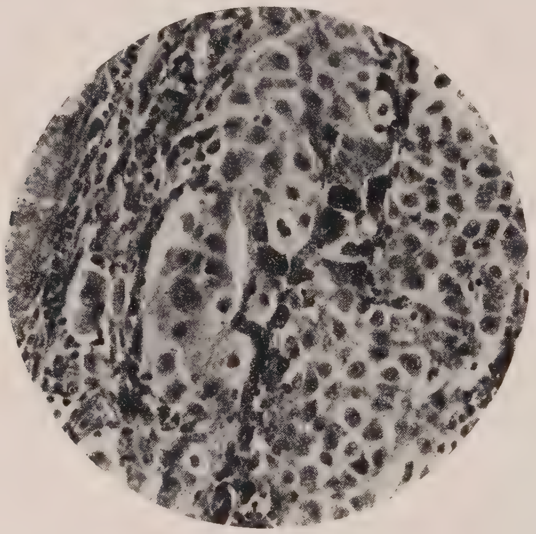

Fig. 164.—Melanoma of Skin, showing the characters of the Cells growing in Alveoli, also Strands of pigment-holding Phagocytes. × 300.

the cells and their arrangement. The cells, which are fairly large as a rule, tend to be polymorphous in type, being rounded, spindle-shaped or irregular in form. In the melanomata of the skin there is usually an alveolar arrangement like that of a carcinoma (Fig. 164), whilst in those of the eye the structural features are sometimes those of a sarcoma. Considerable variations, however, are met with and both types of structure may be seen in the same growth.

Melanomata of the skin show a special tendency to spread by the lymphatics, as well as by the blood stream. The lymphatics in relation to a melanoma may appear as distinct black lines owing to the pigmented cells in their interior, and the lymphatic glands may become enlarged and assume a black colour at a comparatively early stage. The melanoma is one of the most malignant types of neoplasm, as is shown both by the widespread distribution of the metastases and the early period at which they are met with (Fig. 165).

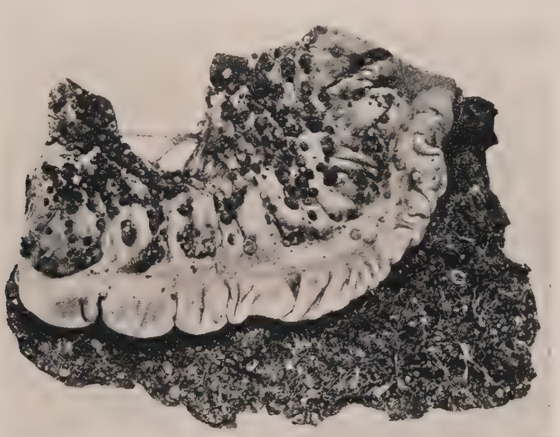

FIG. 165.—Secondary Melanotic Growths in great Omentum.

In connection with the question as to the nature of melanomata, the moles from which they arise are of importance. These moles (also known as ‘ pigmented nævi ’ or merely as ‘ nævi ’) vary greatly in extent, depth of colour and appearance. They may be merely pigmented spots or slight elevations, or they may be rough and warty, sometimes bearing hair. In some instances the epidermis is quite normal, the nævus being situated some distance beneath it and giving a rather bluish colour owing to its being seen through the intervening tissues. If one examines a pigmented mole one finds under the surface epithelium groups or clumps of somewhat small, rounded or polygonal cells of ill-defined character (Fig. 166), with clear protoplasm ; these are known as ‘ nævus cells.’ They may be free from pigment or some of them, especially at the periphery, may contain pigment. The epidermis may be stretched and thinned at the part or, on the other hand, may be the seat of hyperplastic change. The deeper cells of the epidermis may contain excess of pigment or may be free from it. It is from the nævus cells that malignant melanomata of the skin arise, and these are sometimes pigmented, sometimes free from pigment. (It may be noted that pigmented nævi occasionally occur without underlying nævus cells, the pigment being in the cells of the epidermis. The malignant growth arising from such a nævus is an epithelioma.) There has been much controversy as to the origin of the nævus cells, and the question may be briefly considered.

The nævus cells in the ordinary congenital mole may be regarded as 'rests' in Cohnheim's sense (p. 272), but many views have been expressed as to their origin. According to some writers they are derivatives of epithelium, whilst others consider that they derived otherwise. The view as to the epithelial origin of nævus cells was upheld by Unna and it received strong support from the important work of Dawson. The latter observer described and figured in detail the downgrowth of the deep cells of the *rete Malpighii*, their becoming separated off from the epidermis and then assuming the characters of nævus cells. A new light has, however, been thrown on the question by the work of Masson. According to his results, melanomata arise in connection with certain nerve terminations in the skin—the Meissner's corpuscles in the papillæ, the Langerhans' cells (melanoblasts) and the Merkel-Ranvier corpuscles in the epidermis. He has traced the origin of nævus cells to Meissner's corpuscles. At the distal end of a corpuscle the cells form masses and from these similar masses become separated off so that the typical nævus results. Both the corpuscles and the nævi are abundantly supplied by non-medullated nerve fibres, and they also agree in the morphology of their cells and the variability in the amount of pigment contained by them. From the melanoblast of the epidermis (homologue of nævus cell) also melanomata may arise, and there is evidence that in melanomata arising from nævus cells the epidermal melanoblasts may become actively associated.

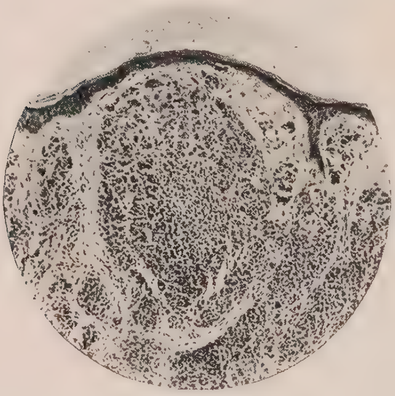

FIG. 166.—Section through pigmented Mole, showing Collections of so-called 'Nævus Cells' underneath the Epithelium. × 75.

There are also in the cutis chromatophores or melanophores; these are histiocytes which have merely taken up pigment. They give a negative 'dopa' reaction (p. 161) and do not *form* pigment—that is, are not melanoblasts. In the malignant melanomata such cells, as already mentioned, actively absorb pigment and become very deeply pigmented.

Masson's view is accordingly that malignant melanomata of the skin arise from nævus cells which are actual or potential melanoblasts, and that these are derived from the sensory nerve terminations in the skin. It is supported by Ewing, Foot, and others. The exact origin of the type cell has not been definitely determined, and Masson does not say whether it is mesodermal or ectodermal. Another point of interest in this connection is that multiple pigmented nævi are often found in association with neurofibromatosis (v. Recklinghausen's disease (p. 803)), another indication of their relation to nerve terminations.

One may say that the malignant melanomata of the skin have the characters of carcinomata but have special features of their own and differ from growths definitely known to arise from epidermal cells, e.g. epithelioma. It is not, however, possible at present to ascribe to them a unitary origin. It is worthy of note that melanoma has been experimentally produced in the dog by repeated application of tar to the skin (Passey).

With regard to the *melanomata of the eye*, the question is rather different. The retinal epithelium contains pigment, and pigment-containing cells are present also in the connective tissue of the iris, sclerotic and ciliary processes. Dawson believed that the pigmented cells of the connective tissue come from the retinal epithelium, and that the ocular melanomata also are carcinomata. Observations on tissue cultures of embryonic eyes have, however, shown that the two types of pigmented cells differ morphologically and also in their manner of growth, and that both have the melanoblastic function. It is also noteworthy that not only do most of the ocular melanomata resemble sarcomata in structure, but the diffuse lymphatic infiltration characteristic of the skin melanomata may be absent. It thus seems probable that some of the melanotic growths of the eye are really sarcomata. If some of the melanoblasts of the eye are of mesodermal origin it appears unlikely that malignant growths may not arise from them as well as from the ectodermal melanoblasts.

ENDOTHELIOMATA

Whilst malignant tumours undoubtedly take origin from endothelium, it is difficult to define exactly the characteristics of an endothelioma. Thus we find considerable diversity in the opinions of pathologists, some considering them rare tumours, whilst others hold that a fair proportion of malignant growths are of this nature. We may say that an endothelioma is a cellular tumour composed of masses of endothelial cells, which infiltrate the lymphatics very much as does a carcinoma (Fig. 167). The cells are rounded or sometimes flattened or spindle-shaped, and there are few or no connective tissue fibrils between them. Accordingly, when one finds a growth *with the structural arrangement of a carcinoma* starting in a situation where no epithelium is present, e.g. a lymphatic gland, and when the cells have none of the characteristic features of epithelial cells, one may be justified in using the term endothelioma; but in many cases one cannot be certain. The cells of such growths have often ill-defined characters, and there are no means by which they can be definitely distinguished as endothelial cells. In the case of the serous membranes, endotheliomata occasionally occur, the pleura being the commonest site. Here the growth often forms a thick layer over the lung, and, microscopically, it presents an arrangement like that of a cancer—alveolar spaces filled with irregularly rounded cells. One meets also with primary tumours of lymphatic glands in which there is a distinctly alveolar structure, and which may be regarded as endotheliomata (Fig. 167). Again, the common fibro-endothelioma of the meninges or meningioma may show infiltrating properties (p. 787), and in such cases the tumour is composed of somewhat plump flattened cells, the arrangement corresponding closely to that of an epithelioma. It must be admitted, however, that in some instances it is quite impossible to differentiate clearly between endothelioma and carcinoma or sarcoma. A malignant growth occasionally takes origin from the vascular endothelium. In such a growth, one can find new formation of blood vessels, and the cells in their walls undergo mitotic division and form solid processes which pass into and blend with the surrounding masses of cells. Such a tumour might be called an *angio-endothelioma,* and is to be distinguished from a sarcoma composed of connective tissue cells, in which there is an associated abundant formation of wide vessels—angiosarcoma or angiomatous sarcoma.

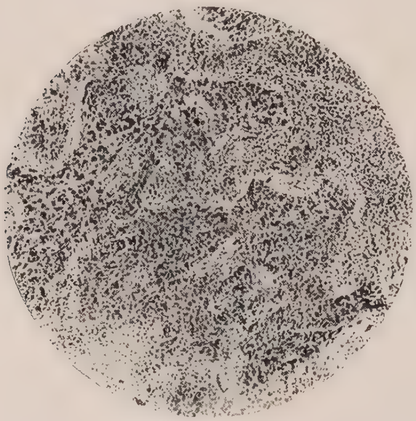

Fig. 167.—Endothelioma of Lymphatic Gland, showing irregular Alveoli filled with somewhat spindle-shaped Cells. × 100.

In some cases the cells of a tumour are arranged as a sort of sheath around the thin-walled blood vessels, although this may be seen only at places; and we believe that such an associated growth of blood vessels and cells is not uncommon. To such growth, the term *perithelioma* is often applied. That the cells take origin from endothelium, however, seems to us an assumption, and it might be better to apply the term perivascular sarcoma. Some consider that they originate from the so-called adventitial cells of the vessels, which are distinguishable, especially by intra-vitam staining, from the ordinary fibrocytes; but this is uncertain. The appearance of perivascular growth may be due to degenerative changes in a sarcoma occurring in the parts away from the vessels.

CYTOMATA OF THE LEUCOCYTE-FORMING TISSUES

It is not possible to give a satisfactory differentiation and classification of tumours which arise from the leucocyte-forming tissues; we shall therefore describe merely the main types. Tumours of this class may be unattended by any increase of the leucocytes in the blood, that is, may occur without the presence of any leukæmic condition. This is the case with lymphosarcoma and myeloma, whilst on the other hand, the chloroma is accompanied by a leukæmic blood picture, and from this condition there are all transitions to leukæmia without any formation of tumour masses. We shall here consider some of the characters of the types of tumours without an associated leukæmia; the growths associated with leukæmia will be described in a later chapter. This arrangement is merely for convenience.

In lymphoid tissue it is generally admitted that there is present a primitive mesenchyme cell which may give rise to the various types of cells—lymphocytes, reticulum cells, endothelial cells of the sinuses or littoral cells, and probably also fibrocytes. Theoretically then, growths may arise from any of these cell types, may vary in their malignancy and may show aberrant cell forms. As a matter of fact the tumours met with fall into one of two classes, namely those composed of small round cells and those of cells rather of the type of stroma cells, like sarcomas or endotheliomas. Recently in view of the relation of the tissue to the reticulo-endothelial system, the terms reticuloses and reticulo-sarcomas have been introduced, the former to indicate enlargements which are not neoplastic and the latter those which are. It is sometimes impossible, however, to draw the line between them. Until some such classification has been definitely recognised it is better to retain terms already in use. ‘Hodgkin's disease’ is one example and will be discussed later (p. 508). An important point about all these growths is that groups of glands are often affected together and this appears to be the result of multicentric origin and not of metastases. The spleen may be similarly involved. In short, we have to deal with system diseases.

The round cell growths are the commoner and of these three illustrative examples may be given. We shall afterwards briefly refer to tumours of the reticulo-endothelial system which are not of the round cell type. The general term reticuloma might suitably be applied to them.

(*a*) Sometimes a tumour may originate in connection with a lymphatic gland and form a slowly growing cellular mass enclosed in a fibrous capsule. Histologically it consists of lymphocyte-like cells in a delicate reticulum, although the structural arrangements of a lymphatic gland are absent. It corresponds with a localised hyperplasia and is often spoken of as *simple lymphoma*. It may remain localised for long and there may be no recurrence after removal.

(*b*) The term *pseudo-leukæmia* is applied when there is a progressive enlargement of lymphatic glands due to increase of lymphocytes, but without the presence of leukæmia. Although the affection spreads and involves various glands, there is little or no destructive infiltration of the tissues around. It is to be noted that such a condition may be followed by lymphatic leukæmia, and accordingly it is probably to be regarded as part of the same affection as the latter.

(*c*) Lastly, there is the *lymphosarcoma* proper, which presents all the infiltrative and destructive characters of a malignant growth (Fig. 168).

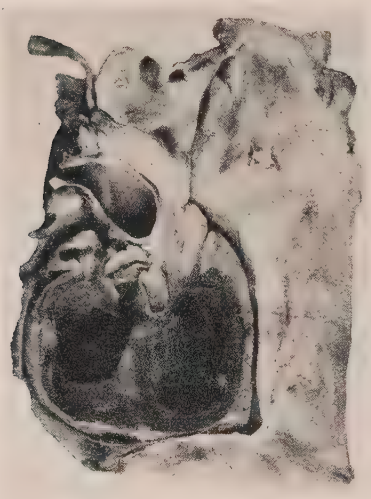

Fig. 168.—Huge mass of Lymphosarcoma of Mediastinum in front of Heart, shown on antero-posterior vertical section.

Lymphosarcoma or Lymphocytoma. This variety may take origin either from lymphatic glands or from other lymphoid tissues. Its commonest site is the cervical glands, though it may occur in connection with other groups. It may occur also in connection with the intestines, where it may produce a diffuse infiltration and thickening of the wall, along with great enlargement of the mesenteric glands. Histologically, lymphosarcoma is composed of small round cells with scanty protoplasm and somewhat resembling lymphocytes or lymphoblasts, but sometimes of indefinite character. Larger cells, apparently derived from reticulum cells, may be present, and occasionally these may become enlarged and have convoluted nuclei. The proportion of the two varieties of cells varies much in different examples of the growth. Between the small cells there is a varying amount of reticulum. The tumour grows rapidly and is usually of pale colour and soft consistence, with a tendency to necrotic softening (Fig. 168). It has a high degree of local malignancy and shows a special tendency to spread by the lymphatics. Lymphosarcoma was formerly believed to be not uncommon at the root of the lung, occurring as a cellular growth with extensive peribronchial invasion. It has now been shown, however, that tumours of this kind are usually small-cell carcinomata arising from bronchial epithelium (p. 429).

Reticuloma. The occurrence of larger cells in lympho-sarcomata has already been mentioned, but there occur tumours in connection with the reticulo-endothelial system, e.g. in the lymphatic glands, spleen, etc., in which the characters of the cells suggest an origin from reticulum cells or endothelial cells. The cells may be rounded, spindle-shaped or irregular in form and may be of large size with aberrant types; in short the growth may resemble a sarcoma, though multiple glands may be affected. Such a growth may be called a reticulo-sarcoma (p. 514). In other growths the arrangement of the cells is in masses, as in an endothelioma, and this may possibly be due to its originating from the sinus endothelium or littoral cells (Fig. 167). The term reticulo-endothelioma may for the present be applied to this type. Some further facts are given in connection with the lesions of the spleen and lymph glands.

The question as to the origin of hyperplasias and tumours of this class from particular cell types is being actively investigated and more definite results will no doubt soon be forthcoming. On the more important questions, however, of their etiology and their relation to one another practically nothing is at present known.

Myeloma. This is a somewhat rare growth, composed of round cells, which originates from the bone-marrow and occurs as multiple nodules; it is unattended by leukæmia. Its characters are described later (p. 519). It is to be noted that this form of growth has of course no relation to myeloid sarcoma, though the term myeloma is sometimes applied to the latter.

OTHER FORMS OF MALIGNANT GROWTHS

Sympathicoblastoma (Neuroblastoma). This tumour resembles the blastocytoma described below, in being composed of embryonic cells, but differs from it inasmuch as the cells are to a certain extent differentiated and recognisable as neuroblasts.

The true nature of this tumour has been recognised only within recent years, and formerly examples of it were classified amongst the sarcomata. The tumour is of very cellular character and often of rapid growth. It is met with in the early years of life and may be present at birth. It is of cellular and hæmorrhagic character and often gives rise to extensive metastases in the various organs, particularly in the liver. The skeletal system is usually also widely affected, especially the skull. Most examples have been in connection with the adrenals, though it occurs also in connection with other parts of the sympathetic system, and it occasionally develops from a ganglio-neuroma (p. 224). On microscopic examination, the cells are round or oval in form and of small size, with little protoplasm round the nucleus. In many parts they are irregularly arranged, while at places they may form small ball-like masses of cells which sometimes show further differentiation into small rings or rosettes, the central part of the ring being occupied by a large number of fine fibrils which give, somewhat imperfectly, the staining reactions of nerve fibrils. The cells surrounding such rosettes are radially arranged, tail-like prolongations of the cytoplasm projecting into the centre forming the fibrillary network (Fig. 169). These structures are closely similar to the clumps of neuroblasts which grow out to form the sympathetic system, as can be well seen in the fœtal adrenal, when it is becoming invaded by neuroblasts to form the medulla of the gland. In view of this fact, and also of the circumstance of their originating in connection with ganglio-neuroma, there can be no doubt that the cells of the tumour are really neuroblasts. It is interesting to note that recently tumours have been described, the origin of which has been traced to the chromaffin cells; to such growths the term *paraganglioma* has been applied (p. 965).

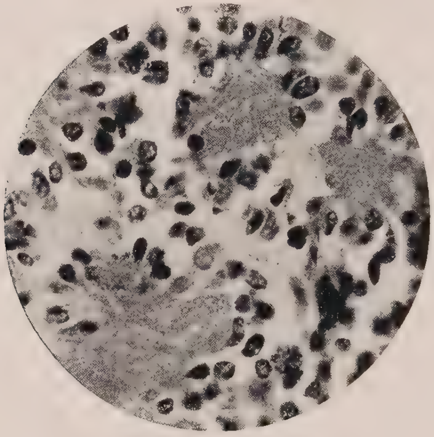

Fig. 169.—Sympathicoblastoma.

Some of the cells are arranged in rosettes with fibrillar material in their centre. (J. S. D.) × 300.

Retinoblastoma. This tumour presents certain analogies to that just described. It is a very cellular growth originating in the retinal layers and its occurrence is usually in the first few years of life. It not infrequently occurs in both eyes (in 23 per cent. of cases, according to Ewing), and a tendency to occur in more than one member of a family is sometimes noted. Occasionally it has been associated with congenital abnormalities in the eyes. It is composed of small rounded or oval cells with very little cytoplasm and of rather undifferentiated character. A somewhat characteristic feature is the presence of small rosettes formed by a circular arrange-

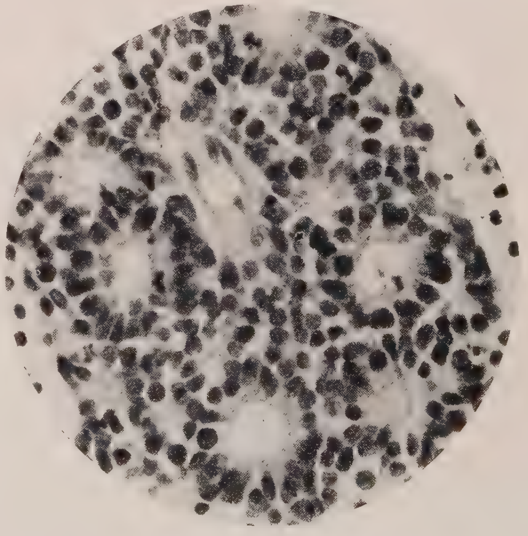

Fig. 170.—Retinoblastoma showing round cells with at places formation of characteristic circles. (Professor M. J. Stewart.) × 400.

ment of cells of short columnar epithelial type enclosing a lumen. (Fig. 170.) In this respect there is a difference from the rosettes in neuroblastoma. The rosettes are present in only a certain proportion of cases, but even when they are absent, the cells of the tumour have not a uniform arrangement and suggestions of such structures may be seen. The growth may extend through the eyeball to adjacent structures and lead to lymphatic infiltration and also secondary growths in other organs. Metastases on the whole, however, occur late and only in a relatively small proportion of cases. The tumour evidently develops at an early stage in the retinal rudiment. It is often known as a 'retinal glioma' but there is no evidence that the cells are of glial nature. It is more appropriately called 'retinal neuro-epithelioma' or 'retinoblastoma.'

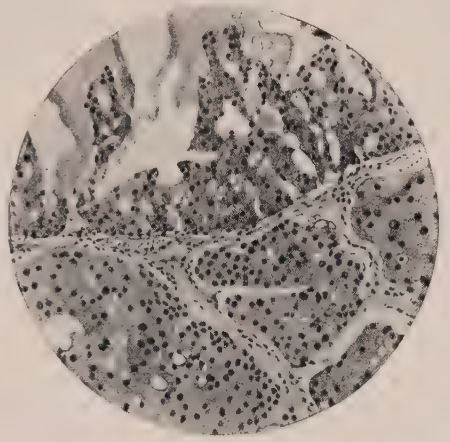

Fig. 171.—Chordoma from Sacro-coccygeal Region, showing masses of Cells in Alveoli with mucoid degeneration in places. (M. J. S.)

Chordoma. This form of growth takes origin from the cells of the notochord, a structure of hypoblastic origin, the remains of which are present in the inter-vertebral discs. It has been met with most commonly in sites corresponding to the extremities of the notochord, viz. in the region of the

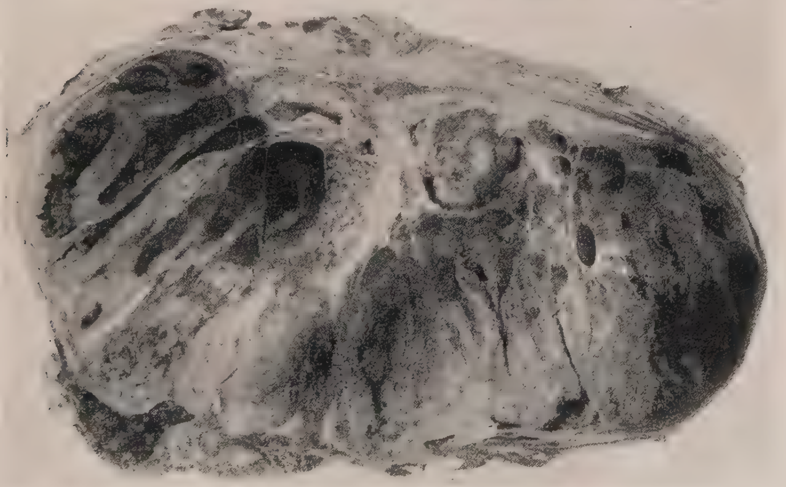

Fig. 172.—Section of Sacral Chordoma.

Note strands and islets of translucent chordal tissue separated by hæmorrhagic areas. × ¾.

spheno-occipital synchondrosis and in the sacro-coccygeal region; but examples have been found in other parts of the spine. The tumour is very rare, and only a limited number of cases have been recorded. At the base of the skull, such a tumour, as it enlarges, soon causes death, but in the sacro-coccygeal region it may grow to a considerable size, and tumours of several pounds in weight have been recorded. The growth is firm and elastic, and appears fairly well circumscribed; on section it shows areas of somewhat translucent tissue (chordal tissue) which tends to undergo softening, whilst between these areas there is a well-formed stroma (Fig. 172). Hæmorrhages are sometimes present in the growth. Microscopical examination shows that the chordal tissue in its earlier stage is composed of somewhat rounded or polyhedral cells of epithelial type, which have the alveolar arrangement of a carcinoma (Fig. 171). But an appearance more of sarcomatous type may be present in the same growth, especially in the case of the more malignant varieties. The cells of the growth form mucin, which is set free and forms an accumulation between them; the cells then become atrophied, and masses of mucoid material with granular remains of cells are left. The tumour may be regarded as one of low malignancy. Secondary growths occur at a late period when the primary growth is large—chiefly in the neighbourhood of the primary growth, very rarely in the internal organs.

III. MIXED TUMOURS

Multiple types of cells or tissues may occur together in the same tumour, and this condition may be brought about in various ways. Occasionally, though rarely, two tumours are really present together, e.g. carcinoma and sarcoma. Ehrlich found that the transmission of a mouse carcinoma from animal to animal might be attended by the development of sarcomatous change in the stroma; a double tumour was then transmissible, and at a later period the carcinoma died out and the growth became a pure sarcoma (Fig. 173). The development of sarcoma in intimate relation with epithelioma as a result of applications of tar or mineral oil to the skin of mice, has been noted by several observers. A truly double tumour of such nature may be met with occasionally in the human subject, but it is very rare, and great care must be taken in interpreting appearances, as occasionally cancer cells may become diffusely arranged and even spindle-shaped. The presence of bone or cartilage in a sarcoma, of course, does not indicate a mixed tumour, but is merely the result of matrix formation by the cells of the tumour which have undergone metaplasia.

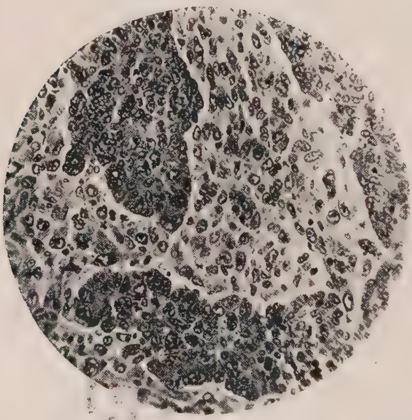

Fig. 173.—Sarcomatous change in Stroma of transplanted Carcinoma of Mouse, resulting in a combination of Carcinoma and Sarcoma. (From a specimen given by Prof. Ehrlich.) × 200.

The most characteristic form of a mixed tumour is that in which the growth takes origin from a multipotent embryonic cell, which has not yet become differentiated and is still capable of producing different tissues ; the term *blastocytoma,* as has been said, may be suitably applied to such a growth. The extreme examples are seen in the case of the teratomata where all the three germinal layers may be represented. We shall describe two comparatively common examples of mixed tumours, namely the blastocytoma of the kidney or nephroblastoma and the 'mixed parotid tumour.' The mixed character is, however, of different nature and significance in the two instances.

Nephroblastoma. This is a cellular tumour in connection with the kidney, which is usually met with in the early years of life, though occasionally it also occurs in the fœtus. Such a growth resembles a sarcoma in its cellularity and naked-eye features generally, but on microscopic examination it is found that, whilst some parts are composed of cellular tissue like sarcoma, in other parts there are cells of epithelial type which are arranged in acini (Fig. 174). And further, at places there may be seen transitional forms between the cells of the acini and the stroma cells. In certain cases there may be also an imperfect development of glomeruli. Occasionally areas of cartilage may be present, formed by metaplasia of the stroma. Metastases of nephroblastoma are of frequent occurrence, particularly in lymphatic glands, liver, lungs, or opposite kidney. We have, accordingly, before us an example of the same cells branching off in different directions and forming different tissues, although such formation is quite imperfect. It should be mentioned too that in certain cases the cells belong to a period further back still in ontogeny, and imperfectly formed muscle fibres, representing the myotome tissue, may be present.

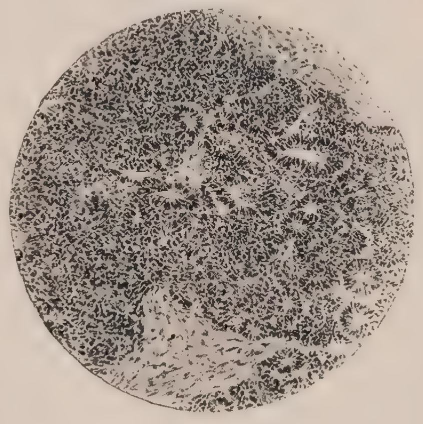
FIG. 174.—Nephroblastoma, showing cellular sarcoma-like tissue with transition to tubular structures. (J. S. D.) × 120.

Mixed Parotid Tumour. This type of growth is commonest in connection with the parotid gland, but tumours of corresponding structure are not infrequently met with in other parts in the region of the mouth, e.g. the lips and palate, etc. The common parotid tumour may reach a large size and produce effects mainly by pressure.

As a rule, it is well encapsulated and does not infiltrate the surrounding tissue, but occasionally true malignant growth becomes superadded. Histologically, the tumour is found to consist both of epithelial elements and connective tissues. The epithelial cells are, in places, of a short columnar type and have an acinous arrangement, but occasionally transition to squamous epithelium may be noted. Further, cells extend from the acini in solid strands which actually become opened out and lost in the stroma, the appearance being as if there were intermediate forms between the stroma cells and the epithelial elements (Fig. 175). The stroma varies considerably in character; it may be a hyaline connective tissue or myxomatous, or again, it may contain islets of cartilage. Such tumours, which are fairly common, probably arise from an abnormality in development, but some observers consider that they originate from adult glandular tissue. In any case it does not seem necessary to ascribe their origin to a multipotent cell. The growth may rather be regarded as an adenoma in which both the epithelial cells and the associated stroma have a special tendency to undergo metaplasia.

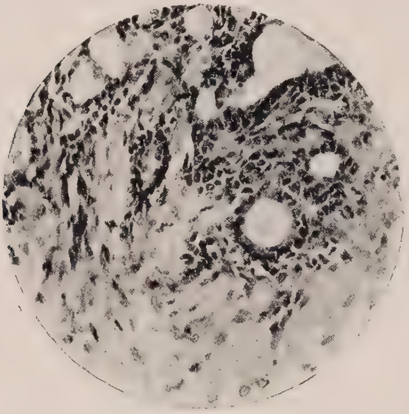

FIG. 175.—Mixed Parotid Tumour, showing acinus-like structures above, the cells of which are giving off strands which merge in the connective tissue. × 200.

TERATOMATA

When identical twins develop from a single fertilised ovum a varying amount of fusion may take place. This may be only of limited extent as in the well-known example of the Siamese twins, or it may affect a considerable part of the body—duplicitas anterior where there is fusion in the posterior region, duplicitas posterior where the anterior region is affected. (Partial fusion of two germinal areas is often spoken of.) Then there are cases where one fœtus is imperfectly represented and is fused with the other, growing on it in parasite-like fashion. All such abnormalities, which are very various, are spoken of as monstrosities. In them very wide deviations from the normal occur; but the formation of parts and the relations of the tissues to one another are well maintained: thus, organs may be doubled or a limb though abnormal in size or form, is still a limb. The subject of monstrosities, however, will not be further considered.

There is, however, a group of abnormalities in which representations of various tissues in the body are chaotically arranged to form a mass, and in the most complicated forms all three germinal layers are represented. Such abnormalities are called *teratomata* ; they are of not infrequent occurrence and are of practical importance. They may be present on the external aspect of the body, the sacral region and the upper jaw being the commonest sites—*sacral teratoma* and *epignathus* respectively ; the former is the more frequent. They are, however, commoner in the interior of the body, especially in the ovaries and testes, though they occur in other parts, e.g. mediastinum, retroperitoneal tissues, etc. They are usually single but occasionally more than one is present. Great variation in naked eye characters is met with, and cyst formation may be a notable feature, as in the common ovarian teratoma (p. 889). There is endless variety in the tissues and in their arrangement. Cartilage, bone, epidermis and glandular epithelium, hair, teeth, etc., are common components, but specialised tissues such as those of liver, kidneys, nervous system, eyes, hæmopoietic tissue and others are also represented (Figs. 176, 177). There is, however, no evidence of the presence of the reproductive glands. Whilst a teratoma may be of such a complicated constitution, there is no proper formation of organs, limbs, etc., and a very important fact is that there is no trace of a vertebral column and no metameric segmentation. It is evident that to such a chaotic assemblage of misrelated tissues the term fœtus, formerly in common use, cannot properly be applied.

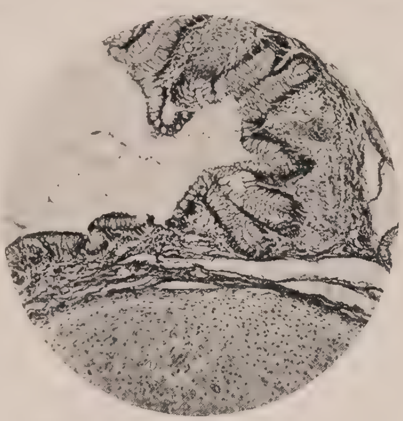

Fig. 176.—Section of Ovarian Teratoma.

Above there is a tube lined by mucin-containing epithelium, and below, a nodule of hyaline cartilage. × 60.

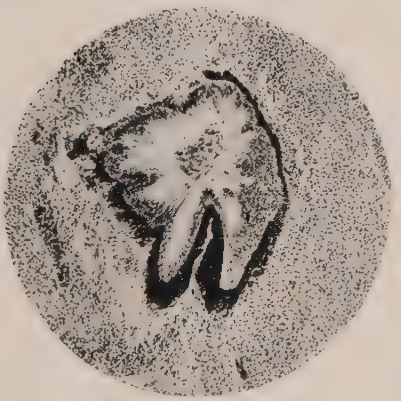

Fig. 177.—Section of Ovarian Teratoma, showing structure composed of tall pigmented cells, apparently a rudiment of the eye. × 60.

In accordance with the facts of embryology it was formerly believed, in view of the complicated structure of teratomata, that they must arise from totipotent cells, and various theories were put forward. The one which received most favour was that teratomata arose from dislocated blastomeres. It is known that in the case of the lower vertebrates a blastomere if separated may give rise to a complete embryo, and this may occur after several cells have been formed by cleavage. No information, however, is available as to whether this obtains also in the human subject. The theory explains well the multiplicity of tissues in teratomata, but the want of any signs of metameric segmentation is regarded as a serious difficulty. Another view is that teratomata are derived from the male or female germ cells. Here something of the nature of parthenogenetic development would have to be assumed, and although this is known to occur in the case of ova under the influence of certain salt solutions, we know of no similar occurrence in the case of male germ cells, as would be necessary for the production of a testicular teratoma. It is interesting to note, however, that Bosæus obtained striking results by stimulating frogs' ova to parthenogenetic development and then placing them in the internal tissues. Under these circumstances tumour masses developed which he describes as having the structure of spontaneous teratomata. Again, it has been supposed that teratomata might arise from fertilised polar bodies but there is no substantial evidence in support of this.

Recent research in experimental embryology has, however, thrown new light on the subject of teratomata. The process of differentiation in ontogenesis has been shown to depend on chemical products of cells called organisers or evocators which act on cells which are susceptible to them, i.e. are 'competent.' The result depends upon these two factors and these vary at different stages of development. Thus there are, on the one hand, organisers of different grades, primary, secondary, etc., and, on the other, the competence of different parts of the embryo, which changes with time. A primary organiser derived from the dorsal lip of the blastopore will evocate a new embryo if brought into relationship with the ectoderm up to the end of the gastrula stage. Or a secondary organiser contained in the optic cups growing from the brain vesicles induces the lens of the eye from ectoderm ; and so on. It is thus evident what a complexity of effects may be produced by the disturbance of such a mechanism. It is maintained that all the known features of teratomata can be explained by the abnormal liberation of organisers of secondary and lower grades and the persistence of competence beyond the time at which it is normally lost. (In the case of monsters primary organisers might be concerned.) The essential element in teratomata is the failure of the individuation field at some early period to control the action of organisers. Another factor in producing complexity is the influence of one tissue in leading to the formation of another. It is believed that from combinations and permutations of such factors, all that is known about teratomata can be produced. This view affords an explanation of the chaotic character of teratomata, but knowledge is wanting as to the primary causes of disturbance in the mechanism of development. The newer work in experimental embryology, however, gives promise of clearing up various problems which have been obscure.

Teratomata are thus the result of chaotic development of structures which may be derived from the three germinal layers. They have not necessarily, however, the essential feature of true tumours—that is, indefinite autonomous proliferation. Some remain without undergoing much change, whilst enlargement of the ovarian forms takes place chiefly by accumulation of secretion within the cyst. Malignant growth may, however, develop in connection with a teratoma, and may be of carcinomatous or sarcomatous type. This is common in the case of testicular teratomata, and metastases often follow. An interesting fact is that, in some examples of mediastinal and testicular teratoma, and in a few instances of ovarian teratomata, chorionic epithelium has been present, with syncytia and Langhans' cells, and from this a chorion-epithelioma has taken origin. Such an occurrence is intelligible if we bear in mind that the chorionic epithelium is a modification of the fœtal ectoderm, and it is another striking example of the variety of fœtal tissues which may occur in a teratoma.

ETIOLOGICAL FACTORS IN TUMOUR GROWTH

Although we are ignorant of the essential biological change in cells when they take on the autonomous character of new growth, certain important factors concerned in etiology are known. It has already been stated that in the case of biological processes causation is usually a complicated affair. We conveniently, however, speak of (*a*) a primary or exciting cause, meaning that particular circumstance in time which starts the process and (*b*) secondary or adjuvant causes, without which the exciting cause would be ineffective. The former usually implies some action from outside the body, the latter a state, as a rule one of varying susceptibility, and this may be inborn or acquired. Without the co-operation of these two factors the particular process may not occur. This is well illustrated in the case of tumours. One often hears the phrase ‘ the cause of cancer,’ but so far as the starting of the growth is concerned there is no one cause ; there are many causes. It has now been shown experimentally that there are many agents which may start malignant growths and these are now usually spoken of as *carcinogenic agents*. These have been proved to be effective when applied to certain *normal tissues*, but we shall have to consider how far their action explains the origin of malignant growths in general. In some instances, malignant disease starts in connection with some congenital abnormality, or occurs at a very early period of life when there is no evidence that a carcinogenic agent is concerned. Formerly too much importance was ascribed to congenital abnormalities, but there are cases to be referred to below where they play an important part.

There is, however, not only the question of the starting of a malignant tumour, but also the question of its subsequent behaviour. Why should its growth be progressive and uncontrolled ? Malignancy may be set up by various carcinogenic agents, but these are not present in the secondary growths. Malignancy is maintained in the absence of the exciting cause. The essential changes in malignant cells must therefore be enquired into—how does a malignant cell differ from a normal cell ? There are thus two questions which must be kept separate though they are often confused, viz. (*a*) the origin of new growths—causation in the ordinary sense and (*b*) the maintenance of malignancy, no matter how it has been started or, in other words, the causation of malignant behaviour.

The subjects to be discussed may be conveniently represented as follows :

(A.) THE ORIGIN OF NEW GROWTHS
    1. Carcinogenic agents and varying susceptibility.
    2. Abnormalities in development.
(B.) THE ESSENTIAL NATURE OF MALIGNANCY
    1. The virus theory
    2. The theory of cellular change.

(A.) The Origin of New Growths

(1) Carcinogenic Agents. Cancer research, as has been mentioned, has shown that malignant growth may be started by various disturbing agents from outside the body, that is by extrinsic causes, aided by the necessary degree of susceptibility. These external agencies as a rule need to act for a long time and their general effect is to cause reactive cellular proliferation. Neoplastic proliferation is thus usually preceded by non-neoplastic proliferation, and the stage during which the latter is going on is often spoken of as a *precancerous* state. This has now been established in the vast majority of cases, but not in all, and is of great practical importance in relation to the prevention of malignant disease. We shall first give an account of some clinical facts bearing on the question and then consider results of experimental work.

Chronic Irritation. It has long been known from clinical observation that this may be followed by malignant disease. Thus epithelioma may be set up in the tongue by the irritation of a sharp tooth or of a clay pipe. It also occasionally becomes superadded to lupus, and not infrequently to such a syphilitic lesion as leukoplakia of the tongue. Old scars may become the seat of sarcoma or epithelioma, and examples of the latter starting from old sinuses used to be by no means rare. Instances of irritation preceding the starting of a tumour are common also in the case of glandular epithelium. Such an occurrence is met with in the case of the cervix uteri and the stomach ; for example, cancer may start in connection with a chronic gastric ulcer. The irritation produced by gall-stones has long been recognised as a condition tending to produce cancer, and many examples of this are met with. In a similar way, though much more rarely, a calculus in the renal pelvis may give rise to carcinoma. The pelvic epithelium may first undergo metaplasia into the squamous type, the growth then being a squamous epithelioma. Many other examples of precancerous states might be cited and the only factor common to them all is the long duration of the irritation ; there is nothing to indicate that the origin of the growth is related to the *nature* of the irritant.

Special Forms of Irritation or Stimulation. Clinical observation furnished strong evidence that some forms of irritation were specially prone to be followed by cancer. The earliest example is the chimney-sweeps' cancer or epithelioma, especially of the scrotum, produced by the irritation of soot. The ova of the *Bilharzia hæmatobia* (p. 704) by irritation produce polypoid vascular nodules in the wall of the bladder, and this condition, which is essentially of a reactive nature, is not infrequently followed by malignant disease. Accordingly, in Egypt where bilharziasis abounds, carcinoma of the bladder is comparatively common. Epithelioma is met with in paraffin workers and in those exposed to the action of tar, pitch and certain mineral oils, the development of the growth being preceded by a form of chronic dermatitis. Epithelioma has been observed to occur in people who have taken arsenic during a long time, the growth following a condition of hyperkeratosis produced by the arsenic. Arsenic epithelioma has been met with also in those who work with arsenic in the preparation of sheep-dip, weed-killer, etc. Cancer of the bladder has been described as occurring amongst aniline-dye workers in Germany and elsewhere ; but it has not yet been ascertained what chemical substance is responsible. The occurrence of epithelioma following exposure to X-rays is undoubted, and there have been a considerable number of cases amongst radiologists. Here also there has usually been exposure for a considerable time, and the rays have a peculiar effect in producing damage to the tissues, which is long-lasting. Recently sarcomata of bone have been observed in some cases of dial-painters, the agent used being luminous paint, which contains radium and mesothorium. These metals are stored in bone, which is thus exposed to all their radiations.

It is to be noted that in most cases malignant growth develops in only a very small proportion of those who have been exposed to the irritant, and also that a long period of time, often ten years or more, intervenes between the first exposure and the appearance of the growth. And another fact of importance is that the growth may occur some years after exposure has ceased. Apparently the irritation causes some essential change in the cells, which may, without further irritation, result much later in malignant neoplasia. These clinical facts, taken as a whole, indicate that certain irritants have a special tendency to give rise to cancer and this has been completely established by experimental work.

The first example of the *experimental production* of carcinoma by a special irritant was announced by Fibiger in 1913. He found that the larvæ of a nematode worm, to which he gave the name *Gongylonema neoplasticum*, by their growth in the wall of the stomach in rats caused epithelioma in a large proportion of cases, occasionally with secondary growths. The real significance of Fibiger's results has, however, become somewhat doubtful. For example, it has been shown that diet, notably deficiency in vitamin A, is concerned in producing some of the results ascribed to this parasite (Passey and others). Some years after Fibiger's publications Bullock and Curtis showed that sarcoma often arose around the cysts of *Cysticerus fasciolaris* in the livers of rats when the animals were fed with the ova of the parasite. (The relation of vesical carcinoma to Bilharziasis has already been referred to, p. 265). Examples of the action of animal parasites as carcinogenic agents are, however, somewhat few.

The most fruitful discovery in experimental carcinogenesis was made by the Japanese workers Yamagiwa and Ichikawa, who showed that the application of tar to the skin for a considerable period might be followed by the development of epithelioma. This result was first obtained with rabbits, but subsequent observations have shown that these animals are relatively refractory whilst mice are specially susceptible. This discovery led to further advances of high importance. There occur first of all thickening of the epithelium and the formation of papillomatous growths with thick cornified layers, and after a time epithelioma develops at the base ; in some cases secondary growths are present. It is to be noted that there are considerable variations in the action of different tars, some being relatively inert. Malignant growths have been produced in mice also by arsenic, pitch and numerous mineral oils, both crude and refined (Leitch), by an ethereal extract of soot (Passey), and by tarry substances prepared from isoprene and acetylene by subjecting them to high temperature (Kennaway). Endeavour was then made to isolate carcinogenic substances in a pure state.

An important advance in this direction was made by the work of Kennaway and his co-workers on the relation of hydrocarbons to tumour growth. Of a large number of such compounds investigated it was found that a certain dibenzanthracene and some related compounds were active in causing malignant growths. Epithelioma in mice and sarcoma in mice and rats were readily produced by means of them ; they have thus a marked carcinogenic property. Peacock obtained similar results in fowls ; he produced sarcomata by subcutaneous injection in a large proportion of experiments. The carcinogenic effect is related to a molecular structure consisting of new rings attached to certain positions of an anthracene ring system. A large number of cyclical compounds have now been prepared and investigated ; some have been found to be carcinogenic whilst others, closely allied chemically, are inert. Of the known carcinogenic agents benzpyrene and methylcholanthrene are probably the most potent as measured by their effects on mice. The former when painted on the skin of mice produces epithelioma in almost a hundred per cent. Such substances are related structurally to œstrone and the sterols (see below).

Browning discovered a styryl quinoline compound which is very effective in producing sarcoma in mice. The dye administered in solution becomes precipitated in the tissues and is then ingested by phagocytes. After a stage of reaction on the part of the tissues lasting a considerable time, sarcoma develops and this is transmissible. This observation is important in showing that the carcinogenic property does not belong exclusively to the polycyclical compounds mentioned above.

A point of importance is that the agents with carcinogenic effect are to be regarded rather as special stimulants of growth rather than as irritants in the ordinary sense. In the various examples given above, a remarkable fact is that the tumour appears within a comparatively definite time in a large proportion of instances. In the case of the lower animals mentioned, it is a matter of months—a relatively long period in the life of an animal ; whilst in the human subject it appears, from clinical facts, to be about as many years. It is noteworthy too that different species of animals show marked variations in susceptibility to such agents. Whilst epithelioma can be produced readily in mice, rats and guinea-pigs have a high degree of immunity. The different tissues also vary in susceptibility, and an interesting example of this is afforded by the fact that sarcoma can be produced in the rat by subcutaneous injection of tar, etc., although it is hardly possible to set up a malignant growth of the skin in this animal.

Relation of Hormones. Cook and Dodds showed in 1933 that dibenzanthracene and some related hydrocarbons had the property of producing the changes of œstrus in mice, and since that time the number of such substances has been added to. There was thus established the important fact that the œstrogenic and carcinogenic properties may be possessed by the same chemical substance. It has also been shown, first by Lacassagne, that œstrone produces in the mamma of male mice changes which may be followed by malignancy ; this is especially so in strains of cancer-susceptible mice, in which, however, spontaneous cancer of the male breast hardly ever occurs (Fig. 178). The changes produced by œstrone are chiefly new formation and dilatation of ducts with hyperplasia of epithelium, also formation of acini, these changes being followed in some instances by malignant proliferation. Injections of œstrone also raise the incidence of cancer in female mice, especially those of high-tumour strains. These facts are especially interesting inasmuch as corresponding changes are often present in the human female breast as an antecedent to cancer. It is to be noted that œstrone does not exert its action locally as in the case of carcinogenic agents in general but on the tissue of the mamma which is specifically sensitive, being carried to it by the blood stream. A wide and an important subject has thus been opened up, but at present one cannot say to what extent disordered hormonic action is concerned in carcinogenesis in the human subject. It is to be noted that though certain substances are both œstrogenic and carcinogenic there is no definite relation between the two properties on a chemical basis. Œstrone and various carcinogenic hydrocarbons are chemically related to the sterols, e.g. ergosterol, the mother substance of calciferol or vitamin D. It has been suggested that carcinogenic substances may be produced from sterols within the body under various conditions but so far this is a matter of speculation.

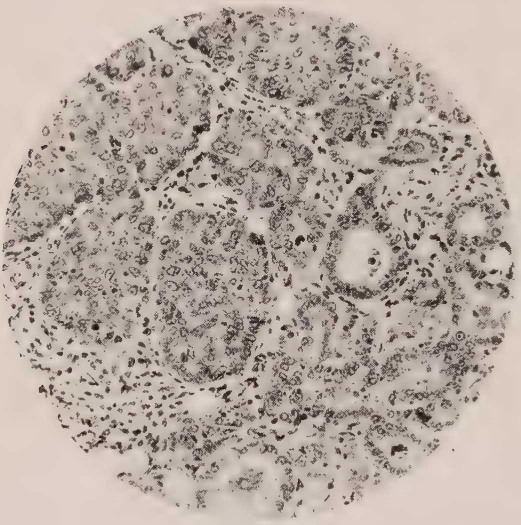

FIG. 178.—Carcinoma of mamma in male mouse produced by repeated injections of œstrone. The carcinoma cells are growing in solid masses.

(From a preparation kindly lent by Dr. A. Lacassagne.)

Radio-active substances, though less used in experimental work, have been conclusively shown to give rise to malignant growths. This is the case with radium mesothorium and thorotrast. The resulting growths have been chiefly sarcomata. Here also a considerable time must elapse before malignancy results. The evidence obtained from clinical cases has thus been completely substantiated.

Although the malignant growths produced by carcinogenic agents have essentially been those of the connective tissues and epithelia most active in repair, success has also been attained with certain of the more specialised tissues—for example, mamma, liver, lungs, bladder and probably also the stomach. The production of carcinoma of the mamma by œstrogenic carcinogens has already been referred to. Carcinoma of the liver was first produced by Yoshida; the growth may arise either from the liver cells or bile-duct epithelium. Such substances produce a gradual destruction of liver cells and this is attended by a hyperplastic proliferation of surviving liver cells which at places passes into malignant neoplasia. Fig. 179 illustrates well such a growth. Such changes are closely similar to those seen in the human subject in the development of liver cell carcinoma in the hypertrophic areas in cirrhosis. Another interesting result has been obtained by Seligman and Shear who inserted pellets of methylcholanthrene into the brains of mice and found that gliomas developed in a certain proportion of cases. No doubt further success will be obtained in the case of other tissues and organs, but the results already obtained demonstrate how important may be the part played by physical and chemical agents in the development of human malignant disease. There are, however, forms of neoplastic growths, especially those occurring in the early periods of life about whose etiology we have no definite knowledge.

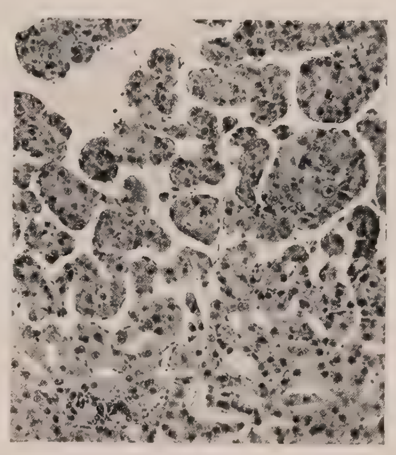
Fig. 179.—Hepatoma experimentally produced in liver of mouse. (Prof. Kennaway.) × 80.

Trauma. This has been a much debated question. In cases of tumour, the history of a blow on the part is not infrequently obtained, but there are sources of fallacy. A blow or slight injury may be the occasion of calling attention to a tumour already in existence; or the patient, noticing a swelling, thinks that there must have been a blow, tries to remember one, and often succeeds. The situations in which tumour is said to be most frequently set up by injury are the mamma, the testicle and the bones; and it is stated by supporters of traumatic origin that the injury needs to be pretty severe. Sarcoma is supposed to start occasionally in connection with a fracture of bone, and some consider that this is a not infrequent occurrence, but it seems that, in the great majority of cases, it is more likely that a tumour already present has weakened the bone and that some sudden strain or injury has led to fracture. In the war (1914–18) there were many thousands of fractures, but we are unaware that there is any evidence of increased incidence of sarcoma as a result. In the case of the mamma, intraduct carcinoma is by no means rare, and it seems to us that an injury might lead to rupture of the wall of a duct and thus allow the escape of the proliferating cells; an ordinary infiltrating carcinoma would then result. In a similar way potentially malignant cells, say in a teratoma of the testis, might be stirred up into malignant proliferation. Whilst the possibility that a trauma may give rise to tumour in such circumstances cannot be denied, we have little doubt that this is a much less common occurrence than is generally supposed. Findlay has shown that epithelioma occasionally arises as the result of a single application of hot tar to the skin of the mouse, the growth appearing several months later; and examples of corresponding nature have occasionally been recorded in the case of the human subject. But so far as we can find, tumour growth has never been produced experimentally by a single mechanical injury.

Relations to Age. Tumours occur at all periods of life, but, taken as a class, are commoner in the later periods. This is especially the case with carcinomata, which usually occur in late adult life. But while this is the rule, their appearance in early adult life or in childhood, is not so exceptional as is generally supposed. Sarcomata are often said to be commoner in young subjects, though certain statistics show that they also are more frequent in the later periods. Osteogenic sarcoma, however, is comparatively rare after the age of thirty. A few definite varieties of malignant growth, whose origin is based on an abnormality in development, such as nephroblastoma, sympathicoblastoma, etc., are met with especially in children, and it is likely that some sarcomata may have a similar origin. On the other hand, the starting of a tumour in connection with a congenital abnormality may not occur till a late period; the development of a melanotic growth from a pigmented mole may be taken as an example. The tendency for malignant growths, especially carcinomata, to occur late in life, is often interpreted as due to a special tendency on the part of the cells at that period to take on malignant properties, and it is sometimes described as being connected with senescence of the cells. In connection with this subject, however, Leitch made the important observation that the experimental production of epithelioma in mice by the application of tar occurs just as readily, and in as large a proportion of cases, in young as in old animals. He found also that when the application of tar is stopped before any growth has developed, malignant disease may appear at a later period. There is, accordingly, the likelihood that the more frequent incidence of cancer in the later periods is due mainly to the fact that the cells have been subjected for the long time that would appear to be necessary for the known or unknown cancer-producing agent to work its effects. Chronic catarrh, irregular growth of epithelium, healed ulcers, etc., all become more common as life goes on, and to this fact the more frequent occurrence of cancer in the later years is mainly due.

Adjuvant Causes—Varying Susceptibility and Heredity. The fact that among a number of individuals exposed to a carcinogenic agent malignant disease affects only a small proportion suggests the importance of varying *susceptibility*, and this is completely established by experiments on animals where the conditions can be definitely controlled. So far as the origin of a malignant growth is concerned, we may say that two chief factors are concerned, viz. (*a*) the carcinogenic agent coming from outside and (*b*) the susceptibility of the tissue ; and the proportion in which these two factors are concerned varies in different instances. An important question with regard to the human subject is to what extent susceptibility may be *acquired*, but on this subject little is known as yet. It is, however, likely that such conditions as vitamin deficiency, endocrine disturbance, etc., may be effective. Some such conditions, however, in themselves lead to structural changes which may be precancerous. The occurrence of œsophageal cancer in the Plummer-Vinson syndrome (p. 462) is an example of this.

Statistical observations on *heredity* have been carried out in the case of mice, and definite results have been obtained. For example, Murray found that the occurrence of spontaneous mammary cancer in mice was more common when there was a history of this growth in the ancestry of the animals than when this was absent. Extensive observations carried out by Maud Slye in America give practically the same result. By in-breeding amongst tumour-bearing mice it has been found possible to obtain stocks in which the natural incidence of tumours is greatly raised. In some instances spontaneous tumours occur in more than seventy per cent. of the females, the vast majority of the growths being adenocarcinomata.

An important observation is that of Brittner who showed that a cancer-producing influence is contained in the milk. Using the young of a high cancer strain of mice, he found that the incidence of spontaneous cancer was much higher when they were suckled by their mothers than when they were suckled by mice of non-cancerous strains. This suggests that something like a hormone is present in the milk, but the nature of the influence is not known. By mating mice of high cancer strain with those of low cancer strain it has been shown that the female has more influence than the male in transmitting the susceptibility to spontaneous cancer. In view of recently ascertained facts it does not seem possible to state whether susceptibility is transmitted on Mendelian principles.

To what extent a hereditarily transmitted susceptibility plays a part in the human subject is an important question, but one which can be only imperfectly answered. Nevertheless certain facts are known. Various clinical observers have been convinced that cancer tends to run in families and this belief has to an extent been confirmed by recent enquiry. Statistical observations in Norway and Holland show that in the case of cancer of the mamma, uterus and prostate, there is a distinct family incidence, cancer in these organs being more frequent in the relatives of those who have had the disease than in the general population. It must be noted that the inborn susceptibility applies to cancer of a particular organ and not to cancer in general. The same fact has been established experimentally. For example, mice of a strain with high incidence of mammary cancer show no increased susceptibility to skin cancer. It may be added that in the case of cancer of the colon in the human subject secondary to papillomatosis (p. 578), retinoblastoma, neuro-fibromatosis, etc., hereditary influence is well marked. With regard to the question as a whole, however, knowledge is still very deficient. External carcinogenic agents are certainly all-important from the point of view of prevention.

(2) Abnormalities in Development

The relationship of such abnormalities to the origin of tumours was especially brought into prominence by Cohnheim, who pointed out that in the course of development groups of cells might be separated or dislocated from their normal relationships, and exist in a dormant condition as 'rests.' Such displaced cells do not carry out their normal functional activity, and he believed that from them tumours often take origin. This view was afterwards extended by Ribbert to groups of cells which might become displaced in extra-uterine life by trauma or disease. He supposed also that in normal circumstances there is a condition of tissue tension, in which the different tissues exert a restraining influence on one another, and that, when the resistance of the connective tissue is diminished, the displaced epithelial cells are prone to take on the properties of tumour growths. That 'rests,' in Cohnheim's sense, are of common occurrence, is certain, but it is not possible to say with what frequency tumours arise from them. Such displaced cells may be portions of adrenal, thyroid, pancreas, gastric or intestinal epithelium, etc., and are often spoken of as 'heterotopias' (Fig. 180). The cells are often differentiated in type and a tumour arising from them would not be distinguishable from one taking origin from the normal tissues. In some

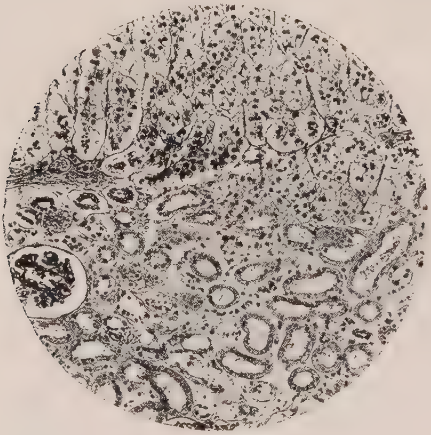

Fig. 180.—Adrenal Rest on Surface of Kidney.

The adrenal tissue is seen above. Capsule of the kidney is partly interrupted. × 60.

cases, however, the origin of a tumour from a congenital abnormality can actually be traced ; in other cases it can be inferred from the position in which it occurs, for example, a carcinoma originating in a site where normally there is no epithelium ; in other cases again from the structure of the growth. The presence of nævus cells under the epithelium in the ordinary mole of the skin has already been described (p. 250) and from them tumours not infrequently arise. Tumours take origin also from persistent fœtal structures which normally become obliterated, for example, growths in connection with the female genital tract from ducts and tubules which normally disappear, tumours at the base of the brain from the remains of the naso-pharyngeal pouch (p. 925), chordoma from the notochord (p. 257), etc. We believe also that adenomata in liver, adrenal, etc., often arise from displaced cells ; and, further, there is the whole group of more complicated growths, including the teratomata, which are the result of abnormalities in development and from which true tumours sometimes arise.

In certain cases, rapidly growing malignant tumours take origin from the cells met with only in the embryo or fœtus. For example, in the not uncommon malignant tumour of the kidney in children (p. 698), the cells can be seen to be differentiating into various tissues, and they represent multipotent embryonic cells (p. 262). So also the sympathicoblastoma is derived from the neuroblasts which grow out and form the sympathetic system. In the central nervous system, tumours may arise from congenital abnormalities of the neuroglia, and it is possible that gliomata usually arise in this way.

It is to be noted, however, that such displaced cells and tissues frequently occur without any development of a true tumour, and, accordingly, just as in the case of adult tissues, there must here be some additional cause which determines the origin. Embryonic tissues are sometimes spoken of as if they resembled tumours in their growth, but the only similarity consists in the relative rapidity in the two cases. As a matter of fact, the developing tissues of the embryo and fœtus are just as fully controlled in relation to one another as are those of the adult. They do not possess in any way the power of unrestrained and independent growth characteristic of tumours. It is possible that cells or tissues displaced either during intra- or extra-uterine life, more readily take on neoplastic proliferation, possibly in some way as the result of want of functional activity ; but it is not justifiable to ascribe more to such displacements. They do not at all explain the great alteration in the habits of the cells when they assume malignant characters. That this alteration may occur in cells at an early stage of their development is the most important fact in connection with this aspect of the subject ; but, so far from throwing light on the origin of neoplastic change, it rather increases the difficulty.

(B.) Causation of Malignant Growth in General: The Essential Nature of Malignancy

The features of malignant growths—their uncontrolled growth, infiltration, formation of metastases—have already been described and have to be considered in connection with this question. It is essential to bear in mind that malignancy may affect any variety of cell capable of proliferation and may occur at any age. Malignancy is so characteristic that we assume for the present that it depends upon one essential cellular change, no matter how it has originated, and this change must be present in the metastases, quite apart from the original exciting cause. Malignant cells can be cultivated outside the body (Fig. 181) just as normal cells can, and behave much in the same way, but the former when re-introduced into a suitable animal show again their invasive properties, whereas the latter simply undergo atrophic change.

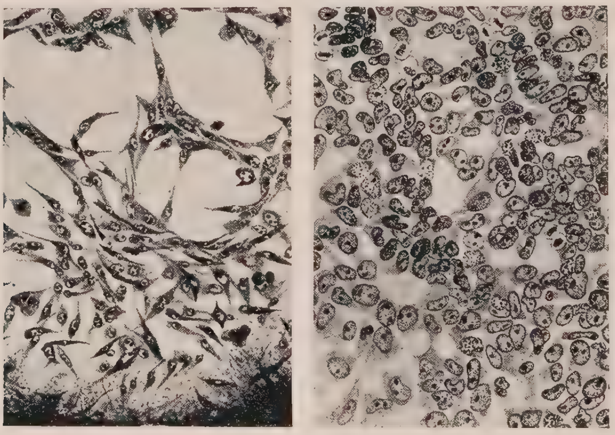

Fig. 181.—Cultures of Tumours *in vitro*.

A, Spindle-cell Sarcoma. B, Carcinoma of Mouse. (Dr. A. H. Drew.)

There are now two main theories in explanation of this characteristic feature of malignancy :—

(*a*) One is that the maintenance of malignancy is due to the presence of a living organism or parasite. This is a theory of old standing and from time to time various organisms, bacteria, protozoa, etc., have been put forward as the cause of malignant growth in general. None of these has stood the test and it is now accepted that there is no causal organism in malignant cells which can be seen by the microscope. Thus if parasite there be it must be ultra-microscopic, that is, a virus. The parasitic theory has thus become the *virus theory*. It of course means that malignant proliferation is merely continued reactive proliferation due to the presence of an organism. If the organisms were removed or destroyed, the proliferation would stop.

(*b*) The other is that malignancy depends on some radical and permanent change in the biological mechanism of the cell concerned, this being evidenced by the characters above mentioned and being continued in successive generations of cells. We may call it *the theory of cellular change.* These two theories may now be considered.

(1) **The Virus Theory.** This theory implies that the various carcinogenic agents above described do not by themselves produce malignant change in cells but merely set up a precancerous proliferation which only passes into the malignant stage when a virus is superadded. In the evolution of this theory the study of certain tumours in the lower animals, especially in fowls, has played an important part, and these will first be referred to.

Up till 1911 it had been found possible to transmit a malignant growth only by means of the living cells of the tumour, that is by transplantation, and only from one animal to another of the same species. In that year, however, Peyton Rous described a spindle-cell sarcoma in the domestic fowl, which could be transmitted by a cell-free filtrate of an extract of the growth and also by the dried tumour cells. The tumours thus produced present the distinctive character of specificity manifested by the tumours which are transmissible by living cells only. Rous subsequently found an osteochondrosarcoma which presented similar properties, and another spindle-cell sarcoma which was transmitted by cell-free filtrate but not by dried cells. Other growths with corresponding characters have been obtained from the fowl by other observers. Fujinami obtained from a fowl a filterable tumour which is transmissible to ducks; and Andrewes found that pheasants also are susceptible. But this does not affect the general significance of what has been said above with regard to specificity. The striking fact accordingly is thus the association of the pathogenic activity of the filterable agent with its relatively specific properties as regards both the animal susceptible and the characters of the tumour to which it gives rise. It must be clearly recognised that the filterable agent is in quite a different category from the carcinogenic agents. It differs from the latter in starting a new growth almost at once and especially in being present throughout the growth and increasing in amount as the growth increases.

The work of Gye,[1] to which much attention has been drawn in recent years, consisted in the first place of a further analysis of what we may call the infective agent in the Rous sarcoma and his fundamental conclusion that two elements or factors are concerned. One of these corresponds in its properties to a living virus, the other to a thermolabile chemical substance. The chemical factor was believed by him to be peculiar to the Rous sarcoma, carrying the specificity, as it

[1] See *The Cause of Cancer*, by W. E. Gye and W. J. Purdy, London, 1931.

were, and was therefore spoken of as the 'specific factor'; while the virus is common to tumours of different kinds. The specific factor is supposed to have the property of so changing a normal cell or breaking down the defences of the cell, that the virus is allowed to act and set up neoplastic proliferation. So far, Gye's view as to the dual nature of the filterable agent has not been established.

Another important question is whether a tumour artificially produced in a fowl, say by dibenzanthracene, contains a filterable virus. Positive results have been reported by McIntosh but confirmation is still required. The results of extensive observation by others have been negative. It is a question, however, which will no doubt be soon definitely settled.

If the filterable agent causing new growth is not of dual nature it must be either a virus or a chemical substance corresponding to Gye's specific factor. Probably the majority of workers in this field regard the filterable agent as a virus; others, however, hold that it is a chemical substance, the product of cells. Amongst the latter is Murphy who has applied to it the term "transmissible mutagen," the term indicating that it produces a definite nuclear change which is thereafter hereditarily transmitted. It is to be noted in this connection that nothing is known with regard to the origin of tumours of the Rous sarcoma type. There is no evidence that in the natural condition the disease passes from animal to animal as occurs in infection. In fact it cannot be said definitely that the filterable agents come from an extraneous source.

Another growth extensively studied in connection with the virus theory is the infective papilloma of cotton-tail rabbits in America, first described by Shope. This is a virus disease which passes from animal to animal in the natural state and can be readily transmitted by scarification. Rous showed that when a portion of the growth is transplanted into the interior of the body of a normal rabbit an infiltrating squamous epithelioma may result. So far these facts correspond with what is known with regard to a carcinogenic agent; but Rous made an additional striking observation. When a rabbit's ear is painted with tar epithelioma does not result, but if after a suitable interval the Shope virus is injected into the circulation an epithelioma develops at the site of application. The virus cannot be demonstrated in the epithelioma, but certain immunological reactions indicate that it is still present. Even if this were so it would not be justifiable to conclude that if the virus were destroyed the malignant growth would cease to progress. Rous holds that the virus is the direct cause of the malignancy itself while others consider that we have to do with the combined effects of two carcinogenic agents which merely start the malignancy. In any case we have to deal with a *specific virus* coming from outside the body and it is difficult to apply the facts to the virus theory in general. A somewhat similar result with regard to the combined action of tar and the Shope fibroma virus has been obtained by Andrewes and others.

Another matter must be referred to in this connection. Recent observations on the viruses of plant diseases have raised the question whether 'the viruses' are living organisms or proteins of large molecules, the products of cells; and necessarily the further question as to the criterion of the living as contrasted with the non-living. Whatever the answer to these questions may be, the all important matter in the case of the virus theory is whether the agent, whatever its nature, has *originally* come from outside the body or has in some way originated from the cells of the body—that is, of extraneous or intrinsic origin. As to this one cannot pronounce.

Up to the present the tumours which can be transmitted by a cell-free filtrate have originated from connective tissue cells or from cells of the leucocyte class. Nearly all have been of the type of sarcoma, although endothelioma has also been observed ; none have been of epithelial origin. This, however, is not surprising as the agent inducing malignancy must be made to act for a time on the cells, and in the case of the epithelia this is a matter of great difficulty.

The virus theory to be generally applicable involves the assumption either that there are a great number of viruses or that there is one virus, which may possibly become modified in a particular way to cause the various tumour growths. In the latter case the question naturally arises as to where the virus comes from. If one paints the surface of the skin of a mouse with tar repeatedly a malignant growth appears after a certain time, and one would have to suppose that the virus is normally present on the skin just as staphylococci are. Again, a sarcoma may result when the tar is injected into the deep tissues of a rat or a fowl, and one might suppose that the virus gets into the body from time to time and is carried to the particular tissue. It seems difficult, however, to imagine that this is the case, seeing that the tumours occur so regularly and after a comparatively definite period ; and difficulty is equally great with regard to the rare malignant growths which arise during intra-uterine life. Recent experiments with regard to the possible source of the virus have been carried out in America by Rous and Botsford. They reared young mice in a protected condition ; that is, they separated them from their mothers as soon as possible after birth and kept them free from contamination of any sort. It is not possible to maintain complete sterility, but it is possible to keep them free from what one might call extraneous organisms of the nature of a virus. After a time, tar was applied repeatedly to the skin of such mice and it was found that carcinoma developed in them just as readily as in ordinary mice. These facts seem very significant and, along with the others mentioned, appear to exclude the possibility of a *virus from outside* being concerned in the production of malignant growths. If the virus does not come from outside, it must be normally present in the body, leading a sort of symbiotic existence, and this is considered to be the case by the supporters of the virus theory in its most recent form. It is supposed that normal individuals harbour this virus and that it becomes active under favourable conditions, such as those produced by carcinogenic agents, etc. This seems to be the only form in which the virus theory can be maintained. At present, however, the known results put forward in support of it are quite inadequate, and moreover it does not seem possible to harmonise them with the known facts with regard to malignancy—in other words to make the theory a consistent one.

(2.) **The Theory of Cellular Change.** If there is no virus present in malignant cells to maintain the uncontrolled proliferation, what is the alternative ? It would appear to be that malignancy simply represents some alteration in the constitution of the cell itself, in all probability a nuclear alteration, this alteration being permanent and transmissible to the cell descendants. This view was advanced in an able manner by Boveri ; he called the altered nuclear constitution " an abnormal chromosome complex," that is to say, an alteration in the elements of the nuclear mechanism which carries the hereditary characters. Such an alteration implies that the cells afterwards produced are likewise changed and that the change is permanent. Similar views have been put forward by others. I have already referred to the fact that a cell in becoming malignant is altered in two ways, viz. in assuming autonomous proliferation and in the acquisition of cell characters, both structural and metabolic, which may vary in different strains of a particular kind of growth. These changes might naturally follow from altered nuclear structure ; they would also be permanent and lead to the reproduction of the characters of the parent cells in their descendants. Theories of this kind are in accordance with the features of malignancy mentioned above ; in fact, they represent a summary of them. They are, however, unsatisfactory as they seem to imply the evolution of a process destructive to the organism, or, as one might say, a failure on the part of nature. Yet it seems that some such theory must be adopted until further research supplies a better one.

Experimental Transmission of Tumours

Reference has already been made to the experimental *production* of cancer. Extensive investigations have been carried out also with regard to the *transmission* of tumours occurring naturally, and many facts of interest and importance have been established. Tumours are found throughout the vertebrate kingdom, though they are commoner in some species of animals than in others. They are not uncommon in mice, and a considerable variety have been met with—epithelioma, carcinoma, sarcoma, chondroma, etc. ; and these animals, on account of their size, have been largely used in investigation. Carcinoma is the tumour of commonest occurrence, and it is interesting to note that it often takes origin from the mammary tissue in old female animals which have been used for breeding. Such tumours can be transferred from one mouse to another by introducing some of the tumour cells into the tissues of a normal animal—in other words, they can be transplanted. It is to be noted, however, that it is impossible to transplant the tumour to an animal of different species, even when it is closely allied, e.g. from the mouse to the rat. Ehrlich believed this to be due not to the active destruction of the cells, but to their failing to find nourishment in an assimilable form in the alien species. To this type of immunity he applied the term *athrepsy* or *athreptic immunity*.

It must be clearly understood that the transplanted cells of the tumour simply continue to multiply like parasites, and that the cells of the new host do not take part in the growth. In the case of a transplanted cancer, the tissues of the new host supply the stroma, which, as has been stated above, is to be regarded as a reactive formation and not a true part of the tumour. In a corresponding way, when the cells of a sarcoma are transplanted, the blood vessels of the host undergo remarkable development and supply the thin-walled vessels of the growth. A tumour, when transplanted, usually breeds true, that is, reproduces the character of the original growth, although certain variations may be met with. Tumours occurring spontaneously vary in their virulence; that is, the percentage of successful transplantations or the rapidity of growth of the grafts varies in the case of different specimens. Reference to the relation of lymphocytes to resistance is made on p. 234.

It has been found also that susceptibility varies considerably in different races of animals. For example, it was found that the English mice were originally less susceptible to Jensen's mouse-tumour obtained in Denmark, than were Danish mice. In the case of transplanted malignant growths, metastases are not so common as in the human subject, but an important point ascertained is that minute metastases may occur and afterwards disappear, the cells undergoing atrophy. Probably a similar occurrence obtains in the case of the human subject (p. 238). The bulk of evidence goes to show that the growth of a malignant tumour is not all-powerful, as it were, but may be modified by comparatively slight changes in the environment.

It has been established that a certain degree of active immunity can be produced on the same principles as in the case of bacterial infection. This result has been obtained by the injection of tumour cells of mild virulence, the animals thus treated and remaining free from growth, being rendered more immune against a virulent tumour. When a transplanted tumour which has grown for some time is excised, the animal may be immune against a fresh inoculation with the same growth, and sometimes even against another type of tumour. This has been called 'concomitant immunity'. It is, however, not of invariable occurrence, as the animal from which the tumour has been removed may be as susceptible to the second inoculation as it was to the first. So also when a transplanted tumour undergoes atrophy and disappears, as sometimes happens, the animal may possess a certain immunity against inoculation with other tumours. The injection of an emulsion of spleen or of the tissues of mouse embryos leads to a certain degree of immunity in mice, and even the injection of the blood of normal mice may have a like effect. The immunity developed by such means is only relative and may be of slight extent: Nevertheless, there is clear evidence that resistance is developed by such methods. Experiments show further that the immunity may be one not only against the particular kind of tumour by which it may be produced, but also against other kinds of growth, so that it is not specific as regards the class of tumour. It is to be noted that in all cases where immunity is produced, this results from the introduction of cells either of a tumour or of normal tissues from another animal of the same species, and these cells must be regarded as being slightly different from those of the animal injected; or we may say that they possess a certain degree of foreignness. It is this difference or foreignness which leads to the immunity reaction which is exerted against the tumour from another animal, and it does not follow that such a method would have any effect whatever in preventing the natural development of a tumour; that is, the immunity would not be exerted against the animal's own tumour. The facts established, and especially the fact that immunity may be produced by normal tissues, indicate that the tumour cells themselves behave as parasites, and appear to be against the view that tumour growth is produced by special parasites.

Relation of Tumours to Radiation. This subject is a very wide one and only the general facts can be stated. In the first place the effect of X-rays and radium rays is one common to normal cells and to tumour cells, though both vary greatly in their sensitiveness. Again, in the case of both, the general statement may be made that the more undifferentiated cells are and the more actively they are dividing, the more sensitive they are. Thus of normal tissues, lymphoid and myeloid tissues and the gonads are most sensitive; probably epithelia of skin and mucous membranes, and thymus come next, while cells of the nervous system are relatively resistant. Amongst malignant tumours the most anaplastic as a rule are most readily affected; on the other hand, the tissues of various simple tumours are as resistant as normal tissues.

In the case of actively dividing cells, say in tissue culture, mild radiation inhibits mitosis, whilst at a later period mitotic division may be increased; abnormalities in mitoses appear, irregular distribution of the chromatin, multiple mitoses, etc. Moreover, Strangeways showed that the young cells may be permanently altered in their characters; some may afterwards undergo degeneration and death. The mitochondria are specially sensitive, becoming granular or vesicular, but one might say that the whole cell complex is affected. Larger doses bring about rapid death of some cells, but, even with powerful radiation, only a proportion of the cells are directly killed. There is also, however, a delayed lethal action, many young cells dying at a later stage.

If we take the case of carcinoma, there are two elements concerned, namely, the tumour cells and the stroma—both are affected. Suitable radiation, say by radium, produces the effects described on cancer cells which are sufficiently brought under its influence, and at the same time causes in the stroma a certain amount of inflammatory reaction. Inflammatory œdema with leucocyte emigration is followed by proliferation of fibroblasts and increased production of collagen fibres, which afterwards become dense and hyaline. An additional important effect is on the small vessels ; many become thrombosed or are closed as a result of proliferative changes in their walls. The result is that the blood supply to the radiated part becomes very much diminished and in this way the nutrition of surviving cancer cells is interfered with. At a late stage the radiated part has become occupied by a dense fibrous tissue in which few vessels are present ; portions of it may have an almost necrotic appearance.

It must be recognised that the direct action on tumour cells occurs only within a certain distance from the source of the radiation ; its intensity is in inverse proportion to the square of the distance. In cases with wide dissemination the possibility of affecting multiple foci is thus an important factor in effective treatment. Experimental work on cancer and also the facts known with regard to the disease in the human subject show clearly that the margin between growth and non-growth is a relatively narrow one, and accordingly a degree of damage to the cells considerably short of lethal effect may lead to their destruction by tissue reaction. On the other hand, there is evidence that unsuitable doses of radiation which fail to lead to destruction of tumour cells may accelerate their growth. Further, when a tumour is repeatedly exposed to radiation, malignant cells which escape destruction may become more resistant, while the stroma reaction may be interfered with.

Variations in resistance to radiation are met with in tumours according to the above principles, but local and other conditions also are concerned. Thus malignant growths of the lymphoid and myeloid tissues and of the ovaries and testes are specially susceptible. Many sarcomata, notably the osteogenic sarcomata, are relatively resistant, but round-cell sarcoma and Ewing's tumour of bone are notable exceptions. Among the epitheliomata again differences are met with, but, as a rule, the most anaplastic types are the most sensitive to radiation ; for example, epithelioma of the cervix uteri is one of the most amenable to treatment. Rodent ulcer also usually disappears readily under radium treatment, even though mitosis in this form of growth is not active. The ordinary spheroidal cell carcinoma of the breast is another anaplastic growth which is relatively sensitive ; adenocarcinomata, e.g. those of the colon, are more resistant. These are merely some general statements, and in relation to treatment various circumstances such as accessibility, the occurrence of multiple foci, etc., as well as sensitiveness of the cells, are of importance.

CYSTS

The term 'cyst' properly means a space containing fluid and lined by endothelium or epithelium. Cysts thus arise by the abnormal dilatation of pre-existing tubules, ducts, or cavities. The contents are usually of a serous or mucoid character, almost colourless or of a yellow tint, and sometimes brownish owing to admixture of altered blood; degenerated epithelium or its products also may be present. The exception to this definition is met with when a cyst loses its lining as a result of inflammatory or other change, and becomes lined by granulation or other connective tissue. The term is, however, often applied in a somewhat loose way to other cavities or spaces containing fluid. For example, the term 'apoplectic cyst' is applied to a space in the brain containing brownish fluid, which has resulted from a hæmorrhage. Tumours sometimes undergo softening in their interior, so that a collection of fluid is formed; this occurs, for example, in gliomata and sometimes in uterine myomata, and the term 'cyst formation' or 'cystic change' is often used in description; 'cysts' of bone belong to the same class. It is advisable, however, that the use of the term 'cyst' should be restricted according to the definition mentioned. Cysts occurring in different situations will be described in connection with the special systems, and we shall here state merely the different ways in which they are formed. The occurrence of cysts in tumours—*cystic adenomata and teratomata*—has already been described. Apart from these varieties we may say that cysts fall naturally into two main groups, viz. (1) those due to congenital abnormalities and (2) acquired cysts, i.e. those produced by lesions in post-uterine life.

(1) **Congenital Cysts.** These again fall into two main groups:—

(A) Cysts may result from *abnormal formation* of organs or parts of the body. Thus multiple cysts may result in the kidneys from an error in development, which disturbs the normal relationships of the tubules (p. 695), and a corresponding condition is met with in the liver. Again, part of an epithelial surface may become detached or dislocated and come to form a cyst. This occurs especially in connection with the skin in the region of the developmental clefts, and the result is a space lined by epidermis and containing sebaceous material, degenerated epithelium, etc. Such a cyst is known as a *dermoid* or *sequestration dermoid*, and the former term should be restricted to cysts of this nature, and should not include the teratoid cysts in which other tissues are present along with the skin and its appendages, for example, the 'dermoids' of the ovary (p. 889). Dermoid cysts are specially met with in the middle line of the chest and neck, at the outer and inner angles of the orbit—in short, along the lines of closure of the embryonic fissures. Occasionally, in the brain a cyst lined by epithelium may be met with, which is apparently the result of dislocation of ependymal epithelium. Cysts occur in connection with the brain and spinal cord, from an imperfect closing-in of structures. Meningocele, encephalocele, and spina bifida belong to this group.

(B) Cysts may be due also to *non-closure of vestigial clefts, ducts, or tubules*, which ought normally to become obliterated in the course of development. A cyst may in this way form from a branchial cleft or from the thyro-glossal duct, urachus, vitelline duct, tunica vaginalis, etc. In connection with the generative organs, cysts of this nature are of frequent occurrence. They may arise from the remains of the Wolffian and Mullerian ducts and also from the remains of the Wolffian body and mesonephros. Examples of such cysts will be given later.

(2) **Acquired Cysts**. These are of several varieties, the two following being the most important :—

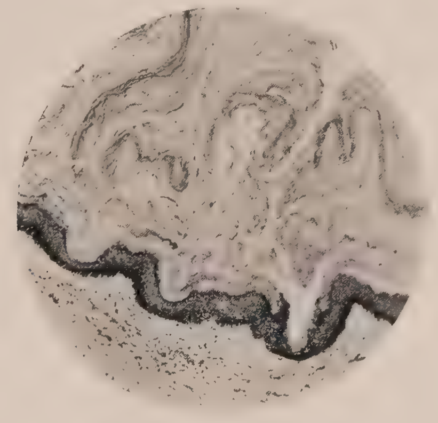

Fig. 182.—Section of Implantation Cyst in Subcutaneous Tissue, showing lining of Squamous Epithelium, contents of separated cells and degenerated material. × 80.

(A) Cysts formed by retention of secretion produced by obstruction to the outflow—*retention cysts*. A single cyst, which may be large, may be produced by the obstruction of the *main duct*, e.g. of a salivary gland, the pancreas, gall-bladder, etc. Obstruction to the orifice of a hair follicle gives rise to a cyst-like swelling filled with sebaceous material, etc.—the so-called wen or atheromatous cyst, met with especially in the scalp. On the other hand, numerous small cysts may result from obstruction of *small ducts*, an occurrence which is not uncommon in the kidney.

(B) Cysts may be formed from natural enclosed spaces, and are then called *distension and exudation cysts*. Cysts may, in this way, form in the thyroid from dilatation of the acini, and occasionally also in the pituitary ; they are common also in connection with

Graafian follicles of the ovaries. Distension of spaces lined by endothelium also is met with ; for example, a bursa may be the origin of a cystic swelling, and there is the common condition of hydrocele due to an accumulation in the tunica vaginalis.

Occasionally, in the adult what is called an *implantation cyst* occurs by the dislocation or separation of a portion of epidermis by injury ; it is known also as an *implantation dermoid.* The epithelium becomes displaced and implanted in the connective tissue, where it grows and comes to line a space which becomes filled with degenerated epithelial squames (Fig. 182) ; rarely hair follicles are present in the wall of such a cyst. Implantation cysts are met with also in connection with wounds of the cornea.

In some examples of cysts, e.g. those in the female mamma, it is doubtful into which of the two categories of acquired cysts they should be placed.

Finally, there are cysts of extraneous origin which are due to cestode *parasites.* The most striking examples are the cysts produced by the *Tænia echinococcus*, though small cysts may be produced in the brain and other parts by the cysticerci of *Tænia solium.*

CHAPTER VIII

CIRCULATORY SYSTEM

I. THE VESSELS

(A) ARTERIES

Lesions of the arteries form a subject of very great importance on account both of their frequency and of the secondary effects which may be produced by them in the various organs. And, as will be described later, serious affections of the brain, heart, and kidneys, which may cause death, are often really the results of arterial disease. It is to be noted that even in the normal condition, changes take place in the arterial tree as age advances, one of the most important being a relative increase in the amount of fibrous tissue; thus the artery of a child consists of a larger proportion of muscle than that of an adult. Such fibrous increase in later years is noteworthy in the aorta and larger arteries, especially in the intima, and these become less distensile and less elastic. The lumen of the aorta, for example, becomes increased quite apart from any morbid change—senile dilatation or ectasia. It has been shown by Andrewes that in the wall of the aorta there is a progressive increase of lime salts as age advances, and this is met with quite apart from any actual calcification. Accordingly, it is not surprising that the alterations associated with the aging of the arteries should be intensified in disease, and we shall see that fibrosis and calcification of their walls are often prominent features. In the pathological changes which are met with, the two main factors concerned are excessive strain, on the one hand, and the effect of toxins, abnormal products of metabolism, etc., on the other hand. Corresponding to these two factors we find changes of a *compensatory* nature and changes which are *degenerative* or retrogressive; and as will be readily understood, these are often combined. We shall consider first of all the alterations which are of the nature of a compensation or adaptation.

Processes of Adaptation and Hypertrophy. It has already been shown how, when an artery is obstructed, there occurs a dilatation of the collaterals, and this is followed by an actual growth of their walls in which all the elements participate. It is an example of compensatory hypertrophy (p. 120), and corresponds in its nature with the physiological hypertrophy of the uterine arteries which occurs in pregnancy.

We shall, however, consider here chiefly the changes which are the result of long-continued *high blood pressure.* The latter may be due (*a*) to contraction of the peripheral arterioles, or (*b*) to actual structural change in them, or (*c*) in the rare condition of polycythæmia, to increased frictional resistance, resulting from increased viscosity of the blood. Without compensating mechanism, the tendency of increased pressure would be to dilate the vessel, and also to produce elongation, as in the case of any elastic tube. These effects are prevented chiefly by the muscular and elastic tissue of the walls, and if the increased pressure continues, a compensatory increase in these elements follows. Thus in the media, which is concerned in regulating the lumen, there occurs an increase of the muscle cells—a medial myo-hypertrophy, and this may reach a considerable degree. In the intima next to the elastic lamina, a few muscle cells running parallel to the course of the vessel are normally present, and in conditions of high blood pressure they undergo increase and often form a prominent feature (Fig. 183). Their function is manifestly to prevent a stretching of the vessel in a longitudinal direction. There is also an increase of the elastic tissue, especially in the intima and adventitia, though it is sometimes noteworthy in the media likewise. The internal elastic lamina becomes thickened, and from it secondary

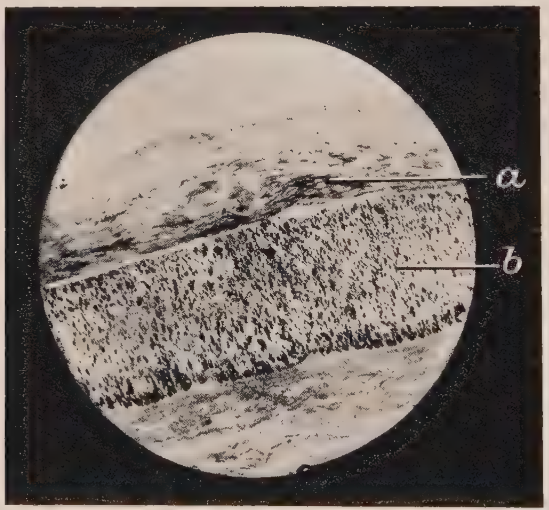

Fig. 183.—Longitudinal section of Hypertrophied Artery, showing Hypertrophy of Muscle in inner and middle Coats.

The muscle fibres are stained darkly: *a*, Longitudinal muscle fibres in intima; *b*, Media. × 60.

elastic layers split off, so that the increase of elastic material may be very marked (Fig. 191).

Such are the *primary hypertrophic changes*, and they may sometimes be well seen in cases of high blood pressure following nephritis in young subjects, where primary arterial disease may be excluded. But in most clinical cases of high blood pressure fibrosis has become superadded. The hypertrophied elements, especially in the media, gradually fail, undergo degeneration and absorption, and become replaced by connective tissue. The result is that the thickened media becomes fibrosed or sclerosed to a varying degree (p. 294), and its elastic tissue may become disintegrated. The general conclusion is that continued high blood pressure brings into operation compensatory increase of muscular and elastic elements, and when these fail *fibrosis with sclerosis* follows.

Another example of adaptation or compensation occurs when there is a local weakness of the vessel; there then follows a thickening of the intima. This is well illustrated in the case of syphilitic lesions of the media (p. 303), which are accompanied by a marked laminated thickening of the intima, and this gives a certain amount of support to the weakened spot.

Thoma explained thickening of the intima in accordance with a principle which he formulated, namely that slowing of the blood stream leads to such thickening. A local weakening leads to bulging and this in its turn to slowing of the blood stream at that point; thus local internal thickening follows. It seems to us, however, that such thickening rather represents a defensive mechanism for giving support. Any local bulging caused by weakness means increased tension at the place in accordance with a well-known physical principle, and unless compensated for leads to further dilatation.

It has thus been shown how the arteries respond to the requirements brought about by special strain, especially continued high blood pressure, how the compensatory changes may fail, and how fibrosis (an inferior type of compensation) may follow. It can be readily understood that arteries thus altered are prone to be the seat of further degenerative changes, fatty, hyaline and calcareous, although these may occur quite independently. Thus a complicated picture often results.

TYPES OF ARTERIAL LESIONS[1]

We shall now give an account of the main arterial lesions, and those of common occurrence may be considered under the five headings of—

(*a*) Fatty Degeneration and Atheroma.
(*b*) Arterio-sclerosis.
(*c*) Calcification of Media.
(*d*) Endarteritis Obliterans.
(*e*) Syphilitic and other Specific Lesions.

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[1] For details, see *Arteriosclerosis*, edited by E. V. Cowdry, New York, 1933.

The three first of these lesions may be said to constitute definite types of arterial diseases; the fourth, on the other hand, represents merely the reaction of the vessel wall to various forms of irritation. The lesions of specific nature will be described separately.

There has been much confusion in the use of the terms *atheroma* and *arterio-sclerosis.* The former is primarily a patchy lesion of the intima with much degeneration, whilst arterio-sclerosis is a diffuse lesion which often affects the whole arterial tree and in which there is usually a combination of hypertrophic and fibrous changes in the arterial wall. No doubt atheroma and arterio-sclerosis, as we have defined them, may occur together; but, on the other hand, either may occur as a practically pure type, and both the nature of the lesion and its significance are different in the two cases. The distinction is of great importance alike from the pathological and clinical points of view. Arterio-sclerosis, in its characteristic type, is accompanied by high blood pressure, and might be called *hypertensive arterio-sclerosis*, or, in view of its mode of production, *post-hypertrophic sclerosis.* It is the condition found in the arteries in what is now generally known as *primary* or *essential hypertension,* and it may also occur as the result of the *hypertension secondary to chronic nephritis.*

The nomenclature is not strictly satisfactory, as the term 'sclerosis' merely means a hardening of the arteries, and this may be produced in more than one way; but as general thickening of the arteries is usually the result of hypertension, it is most convenient to use the term arterio-sclerosis without qualification as indicating the condition stated.

(*a*) **Fatty Degeneration and Atheroma.** A distinction is usually made between these two conditions, but the former may be regarded as the early stage of the same lesion.

Fatty Degeneration, as usually described, occurs in the intima of the aorta in the form of irregular yellowish patches or streaks which are sometimes arranged in a longitudinal direction; they are scarcely raised above the surrounding surface. Occasionally, erosion of their surface may occur. On microscopic examination, they are found to be due chiefly to deposit of fatty material in the stellate cells of the intima and in round cells of the wandering class, also to a certain extent in the endothelial cells. This fatty deposit is mainly cholesterol fat, but a varying amount of glycerol fat is also present. Such patches occur in comparatively young subjects, even in children, and are met with in a variety of conditions—anæmia, cardiac disease, sometimes after infective fevers, etc. They indicate that the intimal cells are prone to undergo degeneration as a result of toxic action and conditions of malnutrition. There is good reason to believe that with a return to health the degenerative changes may be resolved and a normal state of the intima restored.

Atheroma or, as it used to be called, **endarteritis deformans,** is a condition characterised by the formation of patches of thickening of the intima attended by degenerative change. It occurs in arteries of all sizes, but is especially common in the aorta and in various smaller vessels which are poorly supported, for example, the cerebral arteries, coronary arteries of the heart, splenic, etc.

As seen in the *aorta*, the process begins with the appearance of yellowish areas in the intima, which become distinctly raised. These increase in extent and thickness and become confluent with one another (Fig. 184). If a well-formed patch be cut into, it will be seen that the yellow degenerate material is in the deeper part of the intima next to the media, being separated from the lumen by a connective tissue layer of varying depth. Sometimes this layer is thick, and the patch is thus firm and of whitish colour on surface view ; the layer of degenerate material is, however, distinctly seen when an incision is made through the patch. At a later stage, the covering of a patch may give way, and the degenerate material may be discharged into the blood stream, an atheromatous ulcer thus being formed. Lime salts may be deposited in and around the patches, and plates of considerable size may sometimes be formed ; there may be also considerable fibrous thickening. From the combined action of these processes there results great irregularity of the intima ; its surface becomes hard and rough, and at places there may be patches dark in colour owing to altered blood which has soaked into it. The affected aorta often undergoes dilatation and occasionally aneurysm may follow (p. 312). The condition occurs in any part of the aorta, but is usually most marked towards the lower end. The patches are often related to the orifice of branches, and this is especially noteworthy in the case of the intercostal and lumbar arteries, where they sometimes form a double row of button-like thickenings. Lesions at different stages are met with in the same case, thus indicating that the disease is progressive. Atheroma is sometimes associated with calcification of the media (p. 298).

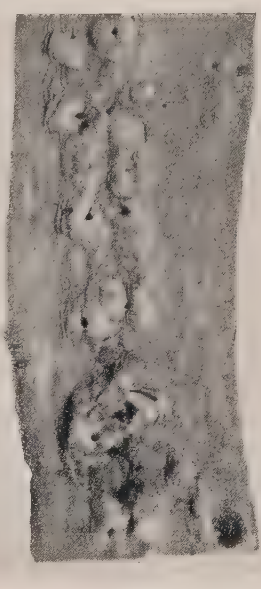

FIG. 184.—Atheroma of the Aorta, showing irregular Patches of Thickening, especially round the Orifices of the Branches.

MICROSCOPIC EXAMINATION of the *aorta* at various stages shows that degeneration and proliferation go hand-in-hand. The lesion starts first, and is always more advanced in the deeper part of the intima, or, as some writers express it, in the *internal musculo-elastic layer*. The superficial part of the patch is composed of thin laminæ of connective tissue with proliferated cells between them. Underneath these, the laminæ become swollen and degenerated and merge into the accumulation of degenerate material in the deeper part. This material comprises globules of cholesterol fat and ordinary neutral fat, especially the former, and albuminoid granules; crystals of cholesterol and fatty acids are common, and lime salts may be deposited in varying degree (Fig. 185). It is noteworthy that a patch of such a nature may be of considerable size, whilst the subjacent part of the media may show little or no change. Fatty change or even fibrosis may affect the superficial part of the media, when the lesion is advanced, but such change is secondary, and, unlike what we find in the case of syphilitic lesions, the lesion is primarily an intimal one.

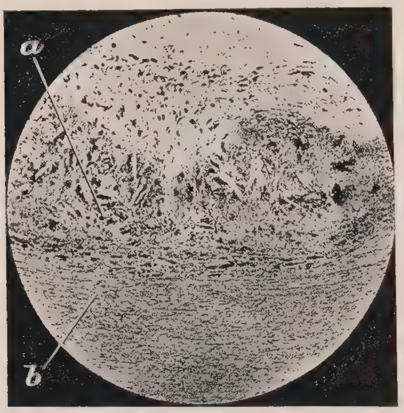

FIG. 185.—Atheroma of the Aorta, showing degenerated material in deeper part of Intima.

The spindle-shaped spaces are due to collections of cholesterol crystals. *a*, intima; *b*, media. × 45.

Atheroma of the aorta, when advanced, may lead to considerable dilatation, especially of the aortic arch. Furthermore, secondary changes may occur in the media to such an extent as to lead to local dilatation and the formation of an aneurysm (p. 312); but in atheroma, as compared with syphilitic disease, the latter is relatively uncommon. Thrombi of various sizes may form in connection with the atheromatous patches, especially when there is any depression, but it is remarkable to what a degree the intima may become thickened and roughened without any thrombosis resulting. Atheroma may lead also to dissecting aneurysm (p. 317).

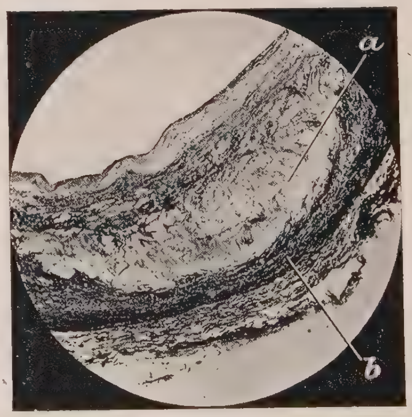

FIG. 186.—Atheroma of Cerebral Artery, showing great Thickening of the Intima with Degeneration in its inner part.

a, degenerated material; *b*, atrophied media. ×45.

Atheroma in the *smaller arteries* is essentially of the same nature—a patchy intimal lesion with fibrous thickening in the superficial parts and degeneration in the deep. A patch is often eccentric, so that the intima has a signet-ring appearance, and it may reach a great thickness, impinging on, and causing stretching and atrophy of the media (Fig. 186). In such a case, the internal elastic lamina becomes greatly stretched and afterwards breaks up into irregular fragments and globules. Ultimately, the media may entirely disappear and the atheromatous patch extend out to the thickened adventitia. The condition of atheroma is shown to the naked eye by the occurrence of opaque yellowish patches of thickening along the course of the vessel. This is especially noteworthy in the case of the cerebral arteries, where the atheromatous areas contrast very markedly with the reddish and somewhat translucent appearance of the normal vessel walls (Fig. 187). Lime-salts are often deposited in the fatty material, and calcification may be so extensive as to change an arterial segment into a rigid tube. This is sometimes well seen in the case of the coronary arteries of the heart.

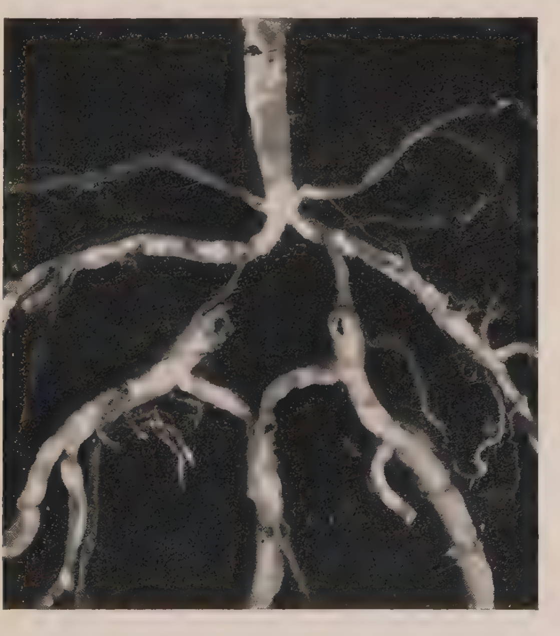

FIG. 187.—Circle of Willis and Branches, showing marked patchy Atheroma.

The *results* of atheroma of the smaller arteries are mainly of a local kind. Thrombosis is not uncommon and the effects of arterial closure follow. Again, an atheromatous patch may lead to considerable diminution in the lumen of the artery and thus to atrophy, which is sometimes attended by fibrosis. In this way atheroma is a fruitful cause of fibrosis of the myocardium, and also leads to cerebral sclerosis in old age. Actual rupture is infrequent but is met with in the small cerebral perforating vessels in the aged. It is to be noted that atheroma may be severe and widespread without leading to high blood pressure and cardiac hypertrophy, although, of course, it may be associated with these conditions brought about by other causes. The distribution of atheroma varies in a remarkable degree, sometimes the aorta and sometimes the smaller vessels being more affected. And in the case of the latter the disease may be specially marked in certain regions.

NATURE AND CAUSATION. A study of the lesions of atheroma at different stages shows that the first change which occurs is degeneration with deposition of fatty material in the deeper part of the intima and that the fibrous thickening is mainly a secondary matter. It may be the result of irritation due to the degenerated material, or it may be of a compensatory nature when the wall has been weakened; and no doubt the general tendency to fibrous increase in the later years of life also plays a part.

As regards the true *etiology of atheroma*, it is not possible to assign it to any one cause, as there are a number of factors determining its onset and distribution. The first of these is *age*. Although fatty degeneration occurs early in life, and intermediate stages to atheroma are found, the latter is essentially an affection of old age, and in its more marked degrees may be regarded almost as a senile condition. Conditions of *local strain* or *tension* seem to be concerned to a certain extent. The distribution round the orifices of vessels indicates at least that a mechanical factor is concerned in its distribution; and the tendency for the disease to be most marked in the lowest part of the aorta is apparently due to the increased hydrostatic pressure in that position. It is also to be noted that atheroma is met with in the pulmonary artery and its branches in conditions of pulmonary engorgement, e.g. in mitral stenosis; but here malnutrition and diminished oxidation may play a part as well as increased pressure. When, however, the relations of the various mechanical factors are considered, it is not possible to make a simple statement. We have found no evidence that long-continued high blood pressure such as occurs in chronic nephritis in young subjects, leads to atheroma, and Aschoff states a similar conclusion. It is thus likely, as he suggests, that something of the nature of a shearing strain, by leading to loosening of the subendothelial connective tissue, is the most important mechanical factor in determining the deposit of the fatty material. It has been considered by some, especially by French writers, that *toxic action* is an all-important factor in the production of atheroma, and no doubt it is at least concerned in damaging the intima. Further, abnormalities in *diet* and *metabolism* may have an influence. For example, it has been shown that when cholesterol, dissolved in oil, is administered in considerable quantities to rabbits, the cholesterol becomes esterised, and doubly refracting cholesterol esters are deposited in various tissues, including the intima of the aorta. The changes correspond closely with those in early atheroma, and proliferation of the connective tissue cells may follow. This is, of course, an extreme condition of alimentation, but the results indicate that metabolic changes may play a part in causing atheroma. It is not possible at present to relate the occurrence of atheroma definitely to increase of cholesterol in the blood. In diabetes, however, in which the latter condition is present, there is a tendency to severe atheroma, from which thrombosis and gangrene may result.

We may summarise by saying that *the intima of arteries is prone to undergo degeneration, as is shown by the fatty change in young subjects, and that this tendency increases in the later years of life and is still further intensified by a variety of conditions—toxic action, strain, abnormal metabolism*, etc.

Other Degenerations. In addition to atheroma in its typical form, the smaller arteries may be the seat of *fatty* and *hyaline* change, variously distributed, especially in old age. For example, fatty change, in which both glycerol and cholesterol fats are concerned, occurs in the walls of the small renal arteries in cases of fibrosis of the kidney, and many of these may be hyaline and have their lumen diminished. So also in the nutrient arteries of the brain, hyaline change, associated with atrophy of the media, may be met with in old age and lead to stretching and rupture of the wall; this may occur sometimes without the presence of high blood pressure.

(*b*) **Arterio-Sclerosis.** The term arterio-sclerosis means a hardening or stiffening of the arteries, and, as already explained (p. 288), is here applied to the condition due to a more or less general increase of the fibrous elements in the arterial walls. The common type is that which is associated with, and mainly due to, increased blood pressure. It may thus be suitably spoken of as *hypertensive arterio-sclerosis*, or *arterio-sclerosis with hypertension*, and in it the fibrosis is associated with evidences of hypertrophic changes. It is also sometimes called *arteriolo-sclerosis*, but this term though indicating one important element in the condition, ignores the fact that the changes are in the whole arterial tree.

Hypertensive Arterio-sclerosis. In this form the walls of the affected vessels become firmer and thicker, and the lumen is often wider than the normal (Fig. 188); the arteries appear to be enlarged generally and they may be increased in length and somewhat tortuous. These changes can be seen specially in the arteries of internal organs, e.g. kidneys or liver, where, on section, the affected vessels stand out prominently as whitish rings. The lumen of the minute arterial branches is, however, often diminished owing to the thickening of the intima. Whilst we have said that this is a more or less general change, it is to be noted that certain arteries and their branches may be much more affected than others; for example, it is not uncommon to find the renal or the mesenteric arteries especially the seat of the change.

Microscopic examination shows that the arterial wall is thickened generally and that there has been a proliferation of connective tissue cells and formation of new tissue, both in the intima and the media (Fig. 191). The extent to which the former is affected varies greatly in different vessels; but, as a rule, it is in the smaller vessels that the intima shows most change, and a considerable amount of concentric fibrous thickening is a common condition. It is to be noted that this may be widespread without the degenerative change of ordinary atheroma. In the thickened media there may be distinct evidence of muscular increase, but in most cases the muscle fibres are found to be undergoing replacement by fibrous tissue, which is more marked at some parts than others, the process ultimately leading to distinct fibrosis of the media. There is, however, no doubt that a true muscular hypertrophy occurs. In cases of arterio-sclerosis in young subjects as the result of primary kidney disease, one has opportunities of seeing an almost pure hypertrophy of the media before the secondary fibrosis has appeared (Fig. 189). Even when there is fibrosis, increase of muscle fibres is often present, and in view of the fact that the lumen of the vessel is usually widened, the increase is greater than it appears. In the thickened intima there is distinct hypertrophy and hyperplasia of the longitudinal muscle layer next the internal lamina (Fig. 183). The muscle cells come to form distinct bundles, and they do not degenerate so early as the circular

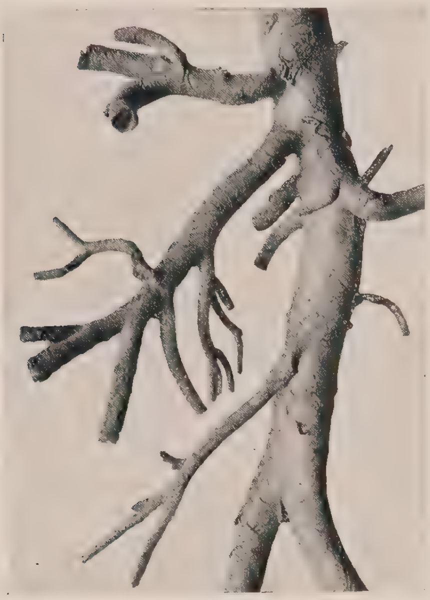

FIG. 188.—Aorta and Arterial Branches from a case of Arterio-sclerosis.

Note the relative enlargement of the branches and thickening of their walls. The patient (æt. 36) suffered from chronic nephritis.

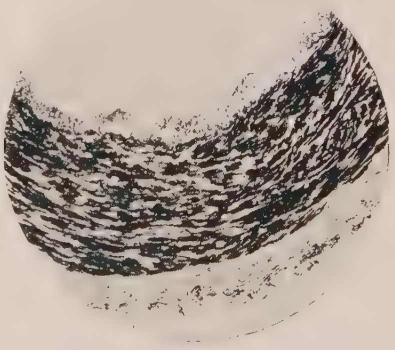

FIG. 189.—Section of Hypertrophied Radial Artery from a case of Chronic Nephritis in a young subject, showing Hypertrophy of the Media.

The muscle fibres appear black. × 60.

fibres. The elastic tissue also shows well-marked hypertrophic change. The internal elastic lamina becomes thickened, and very often new laminæ can be seen in process of being split off, especially inwards towards the intima (Fig. 190). The elastic tissue in the other coats also becomes increased. At a later stage degeneration of elastic fibres occurs, and this is especially seen in the media when fibrosis is advancing, the elastic material becoming granular in appearance and ultimately broken up. We may sum up by saying that in this condition of arterio-sclerosis there occurs a reactive increase of the supporting elements of the vessel wall—muscle and elastic tissue—in response to increased blood pressure; and that this is followed by a gradual degeneration of them, and a progressive fibrosis (Fig. 191). In arterio-sclerosis with high blood pressure hypertrophic changes occur also in the aorta and in the heart. The wall of the aorta is found to be thicker and heavier than normally, and this is due mainly to an increase in the elastic tissue. In response to the increased work, the left ven-

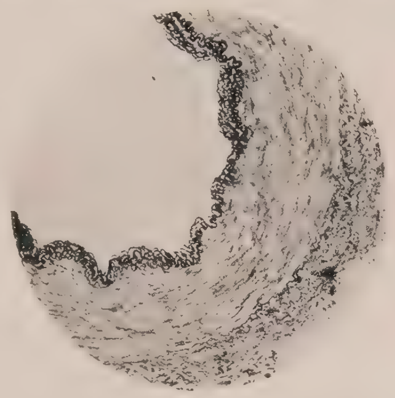

FIG. 190.—Another section of the same Artery as in Fig. 189, showing increase of Elastic Tissue formed by splitting of the Internal Elastic Lamina.

Elastic tissue appears black. × 60.

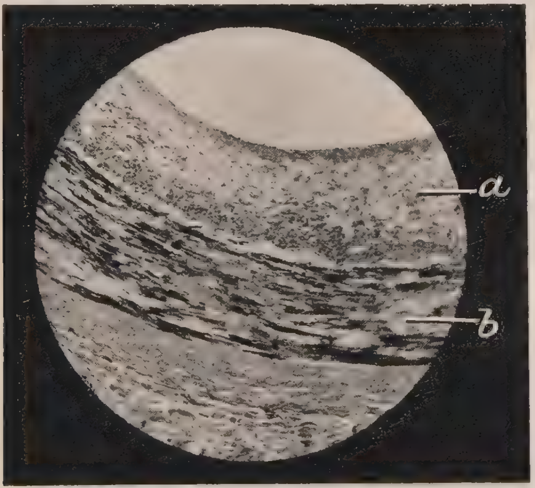

FIG. 191.—Medium-sized Artery in Arterio-sclerosis.

a, thickened intima; *b*, media in which the muscle fibres stained dark are partly replaced by fibrous tissue. × 60.

tricle undergoes a progressive hypertrophy, and in fact the best examples of pure hypertrophy of the chamber are met with in this condition. At a later period when the heart begins to fail, the hypertrophy may be followed by dilatation.

The Small Arteries in Arterio-sclerosis. The changes just described in the arterial tree are to be regarded as of reactive nature—hypertrophic with secondary fibrosis, but there are others in the small arteries and arterioles which are of degenerative type, the results of damage. The walls of certain of these vessels become swollen and hyaline and the lumen may be much diminished ; there is also often fatty change in the wall. Such changes are often seen at a comparatively early stage of hypertension in the kidneys, spleen, etc., their degree and distribution varying in different cases. In the kidneys they are practically always present and lead to atrophic results, as will be described later (p. 670). Further, in some cases there are lesions of more severe type—fibrinoid degeneration and necrosis of the arterial walls, thrombosis, areas of hæmorrhage and tissue necrosis. These latter are an important feature in the so-called *malignant* type of *hypertension.* Evidence that all such lesions are the result of the hypertension will presently be considered.

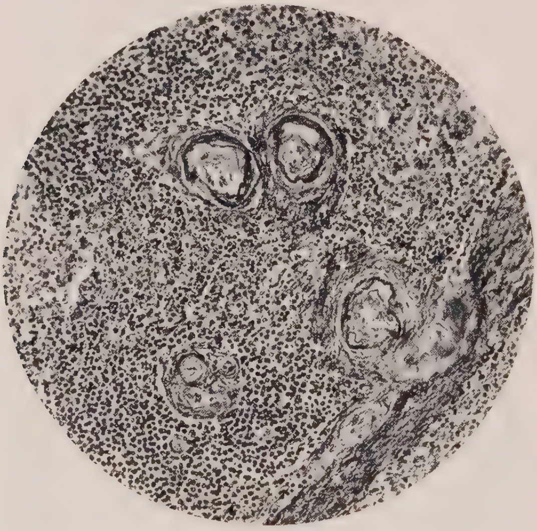

Fig. 192.—Section of Spleen from a case of Arterio-sclerosis, showing great hyaline thickening and sclerosis of small arteries—Arteriolo-sclerosis. × 125.

Etiology. In one group of cases of arterio-sclerosis the hypertension is clearly *secondary to nephritis*, e.g. scarlatinal in the earlier years of life, and the sequel of changes in the arteries can be readily followed, as they occur at an age when primary arterial disease is uncommon. But in the great majority of cases there is no such history, and the arterio-sclerosis is an insidious and slowly advancing affection, and cannot be regarded as secondary to kidney disease. We may accordingly speak of *primary arterio-sclerosis* or the *sclerosis of primary or essential hypertension* in contrast to the form which is secondary to kidney disease.

With regard to the commoner or *primary form of arterio-sclerosis*, two statements may now be justifiably made. The first is that, just as in the form secondary to nephritis, the first occurrence is a hypertonus of arterioles. This is a point of practical importance as it affords the possibility of treatment before actual structural changes have occurred. The second is that all the structural changes, both reactive and degenerative, as above described, can be produced by hypertension. Convincing work on this subject dates from the experiments of Goldblatt, who showed that in the dog partial obstruction of the arterial blood supply to the kidneys caused a maintained hypertension of varying degree. This was especially the case when the arteries to both kidneys were partially obstructed by clamps, or when there was partial obstruction to one kidney and the other was removed from the body. Confirmatory results were obtained by other observers by different methods, but the principle of these is the same. Specially striking are the recent results of Wilson and Byrom. They produced in rats partial obstruction to the artery of one kidney, leaving the other intact, and found that the various types of lesion mentioned above, both the milder and the more severe, occurred in the small arteries in the intact kidney and other organs ; the severity of these apparently depending on the degree of obstruction. They do not occur in the kidney operated on because the partial obstruction of arterial supply protects its vessels against the effects of the hypertension. Renal insufficiency sometimes occurs in such experiments, but it is not the cause of the arterial changes as they may occur when it is not present. An important point is that it is essential that the kidney rendered ischæmic be retained in the body and this suggests that the hypertension may result from some pressor substance absorbed from the damaged renal tissue. All the available evidence goes to show that the hypertension is of humoral or chemical rather than of nervous origin.

It must be clearly understood that these results do not afford definite proof that essential hypertension in the human subject is actually of renal origin. This is a subject for further enquiry and will be discussed later. But they afford convincing evidence that hypertension *per se* may produce all the structural changes in the arterial system met with in the primary form of arterio-sclerosis.

Clinical observation has given little information with regard to the causation of essential hypertension. It occurs in gout and lead poisoning, and has been ascribed to excess in eating and drinking. Hard physical labour may at least exaggerate the condition. A tendency to hypertension sometimes runs in families. In a large proportion of cases, however, none of these factors can be recognised and the etiology is quite obscure. The cause of essential hypertension is still one of the most obscure, as well as most important, problems in clinical medicine.

Results. The small hyaline and fibrosed arteries may give way and cerebral hæmorrhage (p. 724) not infrequently brings about the fatal result. Hæmorrhage from the nose, bowel, etc., is also met with. In other cases the hypertrophied heart fails, and general venous congestion, dropsy of cardiac type, etc., follow. Effects also follow from secondary involvement of the kidneys and are specially severe in the type of the disease known as malignant hypertension, renal insufficiency often occurring. These effects are described later (p. 674). Sclerosis of the coronary arteries, which is often associated with degenerative atheroma, may bring about various serious results—fibrosis of myocardium, infarction, etc.

Arterio-sclerosis without Hypertonus. As has already been mentioned, a pathological degree of fibrosis of arteries without high blood pressure and hypertrophic changes, may be met with, especially in the aged. It is probably to be regarded as a replacement fibrosis consequent on degenerative changes in the elastic and muscular tissues—an exaggeration of the change ordinarily occurring in senile arteries.

(*c*) **Calcification of Media.** Calcification is of frequent occurrence in the arterial system. As described above, it may be in marked degree in the degenerated patches of atheroma, and thus lead to the formation of plates of considerable size. A striking variety of the condition, however, is that which occurs in the media, and which is a not uncommon lesion in old people. It is sometimes known under the name of 'Mönckeberg's sclerosis.' Lime salts are deposited in the direction of the muscle fibres, and hence the affected vessels show transverse streaks or bars, which produce a characteristic appearance (Fig. 193). At a later stage calcareous rings are formed, and ultimately the whole artery may at places be converted into a rigid tube. Along with this change there may be little or no alteration in the intima, though atheroma is sometimes present in addition. The affected vessels on the whole tend to become somewhat dilated. Microscopic examination shows

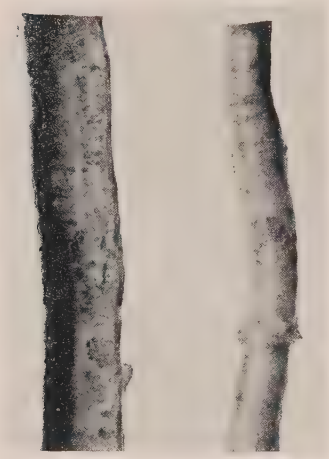

Fig. 193.—Calcification of Media of Iliac and Femoral Arteries, showing transverse markings caused by the calcified portions.

that the earliest change is a sort of hyaline degeneration which affects the muscle fibres and connective tissue, usually starting about the middle of the media (Fig. 194). Thereafter lime salts are deposited first as fine granules, and then continuous calcification follows. There may be little or no cellular reaction along with the deposit. Occasionally actual bone may be formed in connection with an area of calcification, and even the formation of red marrow in the bone has been observed.

Calcification of the media may attack vessels of practically any size. It is commonest, however, in the large arteries, especially the iliacs and femorals, where it may lead to thrombosis and senile gangrene. It occurs also in the lower part of the abdominal aorta, usually in association with atheroma. As to its etiology, little of a definite nature is known. It is essentially a senile change. It may sometimes occur even at a comparatively early period of life in arteries which are the seat of arterio-sclerosis, but it does not appear to be intimately related to high blood pressure, although a closely similar lesion may be produced in the aorta in rabbits by raising the blood pressure, e.g. by injections of adrenalin. The natural increase of lime salts in the arteries of the aged is no doubt another factor. Calcification of the media is to be regarded as a distinct type of lesion, though it may be associated with other forms.

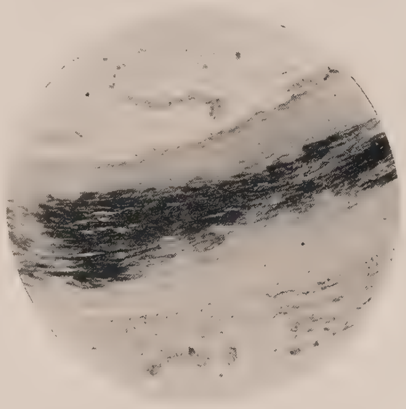
FIG. 194.—Calcification of Media.

The calcification is indicated by the dark staining of the central part of the media. × 30.

(*d*) **Endarteritis Obliterans.** This lesion, known also as plastic endarteritis, represents the ordinary reaction of the arterial wall to an irritant, which often approaches it from without; it is thus hardly to be regarded as a disease of the arteries. It is often to be seen in the neighbourhood of an ulcerative process, such as a gastric ulcer, and it is a defensive reaction preventing hæmorrhage from erosion, which would otherwise occur. Not infrequently it is accompanied by thrombosis. Endarteritis obliterans is seen in silicosis of the lungs as a result of irritation from stone particles around; and it is often a prominent feature in chronic nephritis, apparently due to the hypertension or as the effect of some mild irritant (Fig. 195). Endarteritis obliterans occurs in syphilis in relation to gummata, meningitis (p. 303), etc., though also apart from these, notably in the cerebral vessels. Again, it is often met with in marked degree in tuberculous meningitis when the bacilli settle in the perivascular spaces and damage the arterial wall. The intima may then show enormous thickening, chiefly of a cellular character, and this may be followed by necrosis and caseation of the whole wall.

In endarteritis obliterans there is an abundant formation of connective tissue in the intima, and as capillaries grow into it from the media, degeneration does not follow. The tissue may be comparatively cellular, or it may be more fibrous and arranged in concentric laminæ.

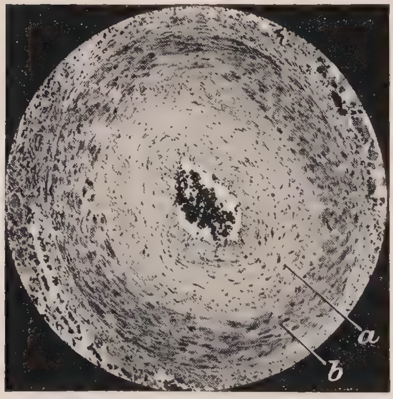

Fig. 195.—Endarteritis Obliterans in branch of Renal Artery in Chronic Nephritis.

a, thickened intima; *b*, media. × 60.

In the thickened intima new formation of elastic tissue occurs. Sometimes there is a distinct lamina under the endothelium and another at the outer edge of the intima, or, again, there may be a number of small laminæ at various points in the intima; and it is to be noted that the new elastic tissue is formed under the influence of the proliferating connective tissue cells, and is not simply split off from the pre-existing elastic tissue, as occurs in arterio-sclerosis. The other coats of the artery show various changes according to the cause which has produced the endarteritis.

SPECIFIC AFFECTIONS OF ARTERIES

In this group the lesions are of chronic inflammatory type and correspond with those met with elsewhere in the respective diseases. By far the most important are those due to syphilis, though in recent years it has come to be recognised that changes of an analogous kind may also be produced by rheumatism. Tuberculosis also may produce arterial lesions in certain circumstances. We have placed other affections in this group because they appear to be due to a specific irritant of organismal nature though the real etiology is unknown.

Syphilis. The most important arterial lesions in syphilis may be said to be the result of endarteritis and periarteritis of the small arteries, in association with infiltration of lymphocytes and plasma cells around them, these changes being brought about by the presence of the spirochætes in the adventitia. This is the case wherever syphilitic disease occurs, and when the aorta is attacked the lesions are essentially in connection with the vasa vasorum, appearing first in the adventitia and then invading the media. Owing to the important results in the latter, the lesion is sometimes spoken of as *syphilitic mesaortitis.* We shall describe first the changes in the aorta and afterwards those in some of the smaller vessels.

The naked-eye changes in syphilitic disease of the aorta can best be studied in young subjects, in whom the disease may occur in a pure form, and the presence of lesions of another character may be practically excluded. The initial visible change is the formation of a plaque or area of thickening in the intima, of greyish-white colour and somewhat translucent appearance. Such plaques are often of considerable thickness and show little or no tendency to degenerate. Later, they extend and fuse together, forming areas with somewhat wavy or slightly wrinkled surface, whilst the intima in the parts between may be healthy in appearance (Fig. 196). At places, absorption and contraction of the tissue may occur with formation of cicatricial tissue which occasionally has a somewhat stellate form. Localised depressions which are potentially the commencement of aneurysms, may sometimes be seen. It is hardly necessary to state that, at a later period of life, the yellow patches of atheroma may be associated with the syphilitic lesions. The aortic arch is by far the commonest site of syphilitic lesions and they are sometimes restricted to it. The part of the arch immediately above the aortic valve is usually involved first and the disease may have two serious results. It may lead to narrowing of the orifices of the coronary arteries or it may spread to the aortic cusps, producing thickening of them and resulting incompetence of the valve. In this way syphilis is often the cause of important cardiac disturbance. The lesions occur, too, at a lower level, but it is not uncommon to find that they cease at the point where the aorta passes through the diaphragm. Sometimes, on cutting through the wall of the aorta, one may find evidence of the extension of comparatively soft, or even gummatous tissue from the outside, but as a rule the characteristic changes in the adventitia can be detected only on microscopic examination.

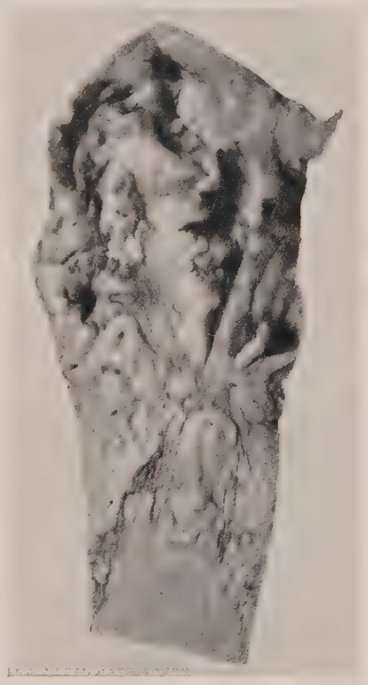

FIG. 196.—Extensive Syphilitic Disease of Aortic Arch, showing the thickened plaques and irregularity of the surface, also formation of aneurysmal patches.

Note the sharp limitation of the disease below. The patient was aged 23.

Lesions of similar character to those described are occasionally met with in the aorta in congenital syphilis and may lead to like results.

As has already been indicated, the earliest histological change to be found is a cellular infiltration around the small vessels in the adventitia, attended by periarteritis and endarteritis (Fig. 197). The infiltration then extends along the vessels into the substance of the media, and at places widens out into irregular cellular areas, in which there is also a new formation of thin-walled vessels (Fig. 198). Such a condition leads to a corresponding absorption of elastic tissue and muscle of the media, and in a section stained to show the elastic fibres, breaks or windows can be seen corresponding to the cellular areas. A certain amount of necrosis may sometimes occur in them; in fact, there may be a small gummatous lesion. At a later period the cellular infiltration is followed by a considerable new formation of connective tissue, and thus fibrous patches or plaques are formed in the media in which no muscle or elastic tissue is present (Figs. 199, 200). It is clear that such changes must produce a local weakening of the wall, and accordingly stretching of the tissue and bulging of the wall are natural results. Thus an aneurysm is frequently started, and we may say that syphilitic disease is the all-important factor in the production of aneurysms of the aorta and large vessels (p. 312). When the changes described are occurring in the media, the intima

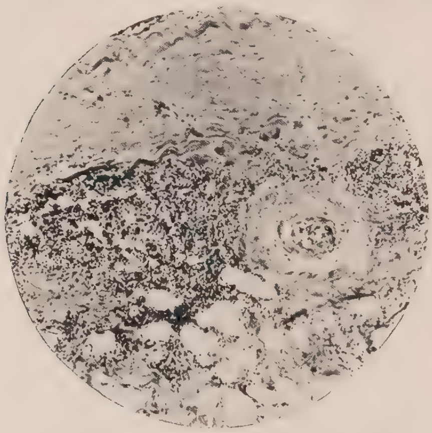

Fig. 197.—Section of Adventitia in Syphilitic Disease of Aorta, showing Endarteritis and Periarteritis of small Arteriole, with fibrous thickening and extensive lymphocytic infiltration around. × 80.

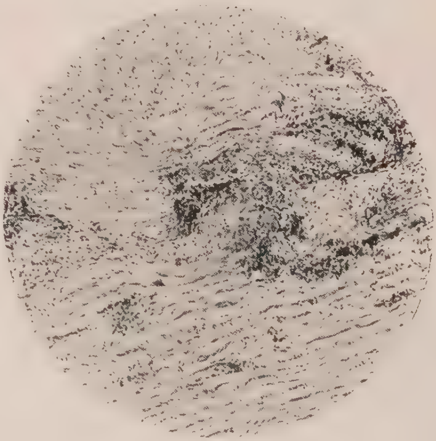

Fig. 198.—Section of Syphilitic Aorta, showing cellular accumulations around the small vessels in the Media, with destruction of the laminæ. × 80.

at the site shows thickening; its connective tissue laminæ become increased in number and are usually swollen. There is often also a considerable ingrowth of new vessels from the media, and this may be concerned in the non-occurrence of degenerative changes. The cellular infiltration present in the other coats rarely extends into the thickened intima, although such extension is sometimes seen. There seems to us to be little doubt that the intimal thickening is secondary to local weakening—of a compensatory or reactive nature, and that it is not part of the syphilitic lesion proper.

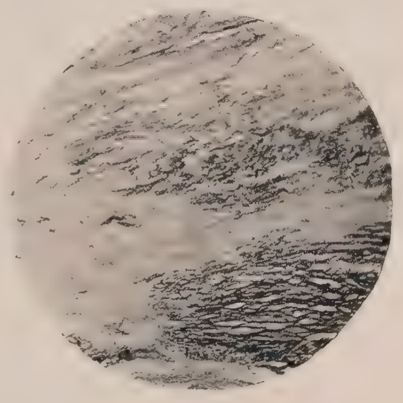

Fig. 199.—Syphilitic Lesion of Media.

The elastic tissue, which appears black, is being interrupted and replaced by fibrous tissue. × 50.

Syphilitic disease of the *pulmonary artery* has been met with in a small proportion of cases. The lesion is of similar nature to that in the aorta, but less in degree. It is occasionally associated with syphilitic disease in the small branches (p. 304).

Endarteritis obliterans is of common occurrence in relation to syphilis. It is a marked feature in all the gummatous lesions, where it is attended by periarteritis; and the obliteration of the small arterial twigs may play a part in the central necrosis which occurs in a gumma. It may, however, also affect blood vessels apart from the presence of gummatous change, and those most frequently involved are the cerebral vessels, the cortical branches running in the sulci often showing the change; a certain amount of meningeal thickening is usually present. In some cases the change is diffuse and a number of the vessels show general thickening, whilst in others it is more of a patchy or nodular type. The walls of the affected vessels are thickened chiefly owing to the increase of the intima, and the thickening may be symmetrical or asymmetrical;

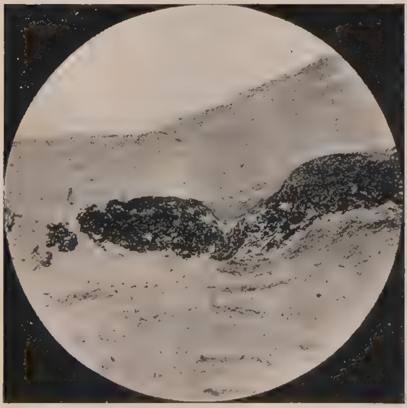

Fig. 200.—Section of Syphilitic Aorta, showing interruption and destruction of the Elastic Tissue of the Media, which is stained black; great thickening of the Intima. × 30.

it varies in degree along the course of the vessel. There is no degeneration, and the vessel walls have a whitish and somewhat translucent appearance. Microscopic examination shows the changes already described (p. 299). One or two giant-cells may occasionally be present in the intima, but these are usually of relatively small size. There is generally infiltration of plasma cells and lymphocytes around the vessels. The obliterative lesion may lead to complete closure of the vessel, or more frequently it may give rise to thrombosis; it is thus a cause of cerebral softening. The term 'gummatous arteritis' is sometimes applied to the usual reactive changes in the arteries in relation to a gumma. On the other hand, it is sometimes restricted to a condition where there is an actual extension of the gummatous tissue into the arterial wall, the latter becoming involved in the necrotic change.

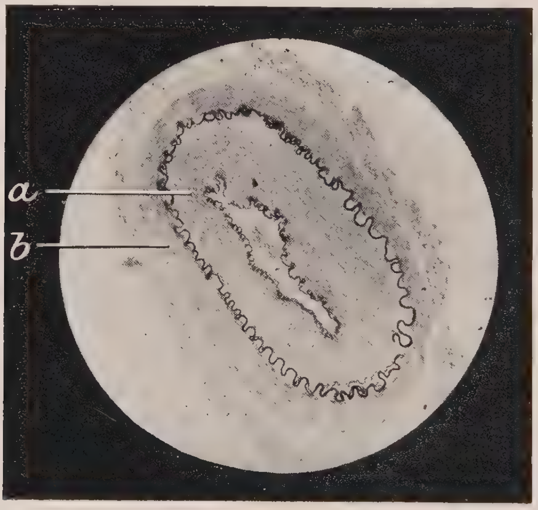

Fig. 201.—Syphilitic Endarteritis and Periarteritis in a Cerebral Artery.
The greatly thickened intima is seen between elastic laminæ which appear black: *a*, intima; *b*, media.

Corresponding syphilitic lesions in the minute *pulmonary arteries* in some cases have been found. They are essentially of the same nature—endarteritis and periarteritis with a certain amount of infiltration of lymphocytes and plasma cells. They may be widespread and are often attended by a diffuse or nodular fibrosis. Serious obstruction of the pulmonary circulation, cyanosis and polycythæmia are produced; there is hypertrophy of the right side of the heart with its accompaniments. There is often marked atheroma of the larger branches of the pulmonary artery, apparently the result of the increased pressure and anoxæmia. Syphilitic disease of the pulmonary artery itself has been observed in a few instances.

It may be mentioned here that similar obstructive changes in the small pulmonary arteries may sometimes occur apart from syphilis. An example of this is a disease occurring in the Argentine, described by Ayerza and named after him. Quite a number of cases have been recorded and in some of them the cyanosis has been extreme. Lesions of similar nature have been met with from time to time in other places. Nothing is known of the etiology of cases of this type where syphilis as a cause is excluded. *Obliterative pulmonary arteriolitis* would be a suitable descriptive name.

Effects of Syphilitic Disease. These have already been mentioned in the description but they may be conveniently summarised. In the aorta the most serious results are (*a*) aneurysm (of which syphilis is by far the commonest cause), (*b*) implication and consequent narrowing of the orifice of a coronary artery by a syphilitic patch (p. 335), and (*c*) spread of disease to the aortic cusps with resulting incompetence of the valve (p. 351). Occasionally embolism may occur from a thrombus on a syphilitic patch or in a small pouch in the aorta. The effects of the disease of the small arteries are seen mainly in connection with the brain and are caused by narrowing and sometimes closure of the vessels. Thus ischæmia and cerebral softening are often produced (p. 729). Occasionally necrotic change in a gummatous patch may involve an artery and its wall may give way, but in our experience syphilis plays no important part in the causation of cerebral hæmorrhage.

Rheumatic Lesions. Within recent years it has been shown, especially by the work of American pathologists, that lesions are produced by rheumatism in the walls of arteries, of corresponding nature to those found in the heart. Such lesions have been found especially in the aorta, though they have also been described in smaller vessels. Just as in syphilis, the nature of the lesions points to a distribution of the infective agent by the perivascular lymphatics. In the aorta the lesions commence in the adventitia and consist of an infiltration of the tissues with lymphocytes and plasma cells. Here and there may be foci of more marked reaction of histiocytes, and typical Aschoff bodies with characteristic cells (p. 332) may form. The cellular infiltration may spread into the media and lead to absorption of elastic tissue, but this rarely extends beyond the outer third of the media. No evidence has been adduced that such lesions become sufficiently pronounced to lead to weakening of the wall and to aneurysm. In judging as to their rheumatic nature the possibility of their being due to syphilis must, of course, always be kept in view.

With regard to the smaller arteries, the lesions have been found especially in connection with the smaller visceral branches, their distribution varying much. They are said to be of more acute character and may be accompanied by a certain amount of necrosis of the media as well as by leucocyte infiltration; they thus resemble somewhat the lesions of polyarteritis nodosa. Nevertheless, aneurysmal dilatation has not been found to follow, nor has thrombosis within the affected arteries been observed. Further work is necessary before it is possible to estimate the relation of rheumatism to disease of the smaller arteries. No such relation has been established on clinical grounds, though the occurrence of focal lesions in the subcutaneous tissues and elsewhere shows the widespread distribution of the infective agent.

Tuberculosis. We have already mentioned the occurrence of marked periarteritis and endarteritis in relation to tuberculous lesions. They are often a prominent feature in tuberculous meningitis and may lead to complete obstruction of the vessel and softening of the brain substance. A corresponding condition is met with in tuberculous disease of bone, where the involvement of an artery may lead to an area of necrosis and the formation of a sequestrum ; this occurs especially underneath an articular cartilage, as will afterwards be described (p. 815). The extension of tuberculous ulceration in pulmonary phthisis leads, of course, to an extensive destruction of blood vessels, and these become obliterated in the manner described, as the ulceration extends. Occasionally, however, an artery in the wall of a cavity may have its wall weakened before obliteration occurs ; it then yields and an aneurysm may form (p. 421). Tuberculous infection has been observed in an atheromatous patch of the aorta with formation of thrombus, in which tubercle bacilli have been found, but it is very rare ; occasionally a similar lesion has been met with in an aorta without atheromatous change.

Thrombo-angeitis obliterans.[1] This term was applied by Buerger in 1908 to a somewhat uncommon affection which is characterised by the occurrence of progressive lesions in the arteries with secondary thrombosis. It is met with at a relatively early age, being not uncommon before forty, and the pathological changes show that it is distinct from both atheroma and arterio-sclerosis. The clinical features are somewhat characteristic and depend upon the extensive occlusion of the arteries by thrombi. Gangrene often supervenes, necessitating amputation, and amputated limbs have usually supplied the material for examination. On examination of such a limb one usually finds many arteries completely closed. The thrombi are for the most part completely organised and many are permeated by comparatively wide vessels (Fig. 202) ; others again show changes at an earlier stage. The condition of the arterial walls varies greatly, but there is usually considerable fibrosis of the media and adventitia (Fig. 203), and an important feature is that the fibrous overgrowth may extend for a distance around, involving nerves, muscle fibres, etc. In some arteries there may be considerable endarteritis without thrombosis. A rather striking point is the occurrence in the thrombi of focal accumulations of cells with giant-cells in the central parts, the appearance resembling that of tubercles. Similar changes may be present in the accompanying veins, many of these being filled with organised thrombi, and Buerger has described a migrating phlebitis affecting the superficial veins in a certain proportion of cases. All these changes are, however, at a comparatively late stage of the disease, and Buerger considers that they are the sequels of an earlier more acute stage which he has found in some instances. In these he describes an infiltration of the arterial walls by polymorphonuclears and also accumulations of these cells in the thrombi, which are afterwards replaced by granulation tissue with giant-cells. It remains to be determined to what extent this is the ordinary sequence of events, and certainly a point requiring elucidation is the *progressive* character of the chronic inflammatory process.

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[1] *The Circulatory Disturbances of the Extremities,* by L. Buerger, Philadelphia and London, 1924.

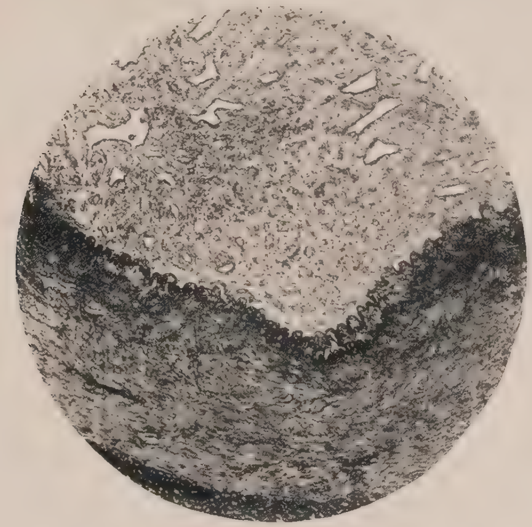

Fig. 202.—Section of large Artery in Thrombo-angeitis Obliterans.

The lumen is occupied by an organised thrombus in which numerous newly-formed blood vessels are seen. (G. McC.) × 40.

The symptoms are varied and depend on the degree of arterial obstruction. The earliest are pain, disturbances of sensation, and circulatory disturbances—local redness, which disappears on elevating the limb, formation of vesicles, etc. On walking there is often cramp-like pain and inability to progress

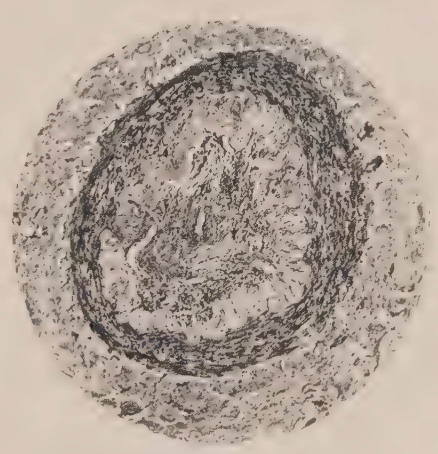

Fig. 203.—Thrombo-angeitis Obliterans, late stage.

Lumen of artery is filled by vascularised thrombus and there is much fibrosis in the wall of the vessel. (G. McC.) × 60.

—'intermittent claudication'; this is a result of imperfect blood supply and may be met with in other forms of arterial disease. Later, more severe trophic changes appear, intractable ulceration, and gangrene which is apt to spread slowly; amputation, sometimes repeated, is often necessary. In view of the widespread involvement of the arteries it has now been recognised that amputation should be performed at a high level. The disease affects the arteries of the lower limbs in the great majority of cases, and it is only rarely that those of the arms are involved. The effects which we have mentioned thus usually appear first in the feet (Fig. 204).

The disease has been observed almost exclusively in males (in 99 per cent. of cases, according to Buerger), and it often starts before middle adult life, certainly earlier than the period of arterial degeneration. Its prevalence among Jews was at first supposed to be a special feature, but subsequent observation showed that the disease has a widespread distribution as regards both locality and nationality. The facts established point to the disease being one with specific etiology, caused by an irritant which apparently spreads and thus is probably of organismal nature; but so far no organism of any kind has been found and no relationship to syphilis or any other disease has been established.

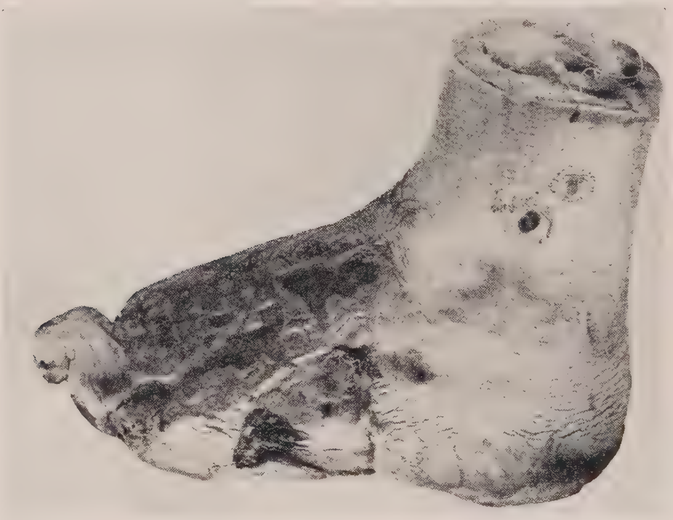

FIG. 204.—Foot from a case of Thrombo-angeitis Obliterans, showing Ulcers and loss of Toes from Gangrene.

Periarteritis Nodosa or Polyarteritis Nodosa Acuta. The latter is the preferable term, as it distinguishes this rare affection from nodose periarteritis caused by syphilis (p. 303). The essential feature is a focal periarteritis with involvement of the media and a tendency to the production of aneurysms. The condition is on the whole commonest in adult life, and is more frequent in males than in females. The disease runs a relatively rapid course and death is usually produced by hæmorrhage. The lesions are especially common on the visceral arteries, e.g. coronary arteries of the heart, renal, splenic, mesenteric, hepatic, etc., and are indicated by the presence of nodules or patches of thickening along the course of the blood vessels. Aneurysms at various stages of formation may be present and comparatively numerous. On microscopic examination it is found that in the affected parts there is a subacute inflammatory lesion with extensive infiltration of leucocytes in the adventitia, and that, along with this, there soon occurs a necrotic change in the adjacent media. The necrosis rapidly spreads inwards, so that the whole thickness of the wall is involved. A certain amount of compensatory proliferation may be found in the intima, but this rarely reaches a marked degree. Then follows a stretching of the degenerated and necrotic tissue, and an aneurysm soon forms (Fig. 205). With regard to the etiology nothing definite can be said. It appears certain that the affection is not of syphilitic nature, and no characteristic organisms have been found in the lesion. The picture, however, is that of some unknown infective agent spreading along the perivascular lymphatics and producing the changes described in the adventitia and media.

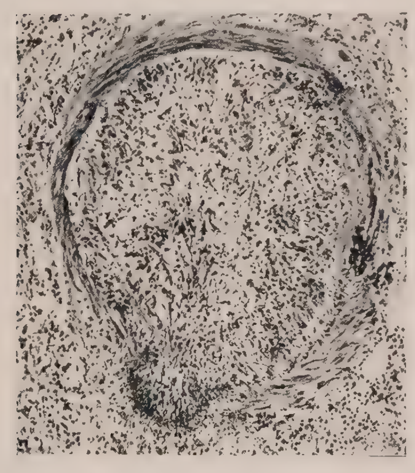

Fig. 205.—Polyarteritis nodosa acuta. Small artery in kidney showing inflammatory change. Note small aneurysmal bulging below. (Dr. Janet S. F. Niven.) × 100.

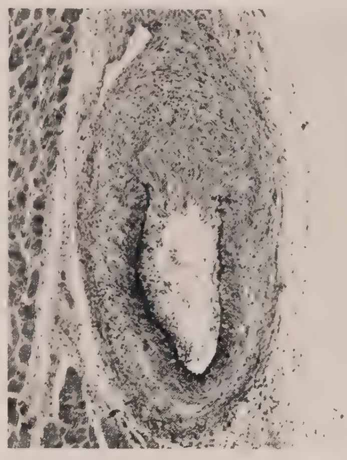

Fig. 206.—Polyarteritis nodosa of less acute type affecting branch of coronary artery of heart. Note excentric character and rupture of elastic lamina. (J. S. F. N.) × 50

The description given is that of the disease in its acute and more intense form, but there are also cases in which the affection runs a more chronic course and these are much commoner. In them the damage to the walls of the arteries is followed by reparative proliferation which compensates for the weakness, and in this way aneurysm formation may be avoided. The result is that the formation of nodular thickenings along the arteries is the chief feature, and these may be accompanied at places either by a certain amount of dilatation or by diminution of the lumen up to complete occlusion. Such changes are met with mainly in the visceral arteries and vary greatly in distribution in different cases. The arteries of the kidneys and heart (Fig. 206) are most frequently affected and in these organs fibrotic atrophy or infarctions follow, according to the degree of obstruction. In the former considerable irregularity of surface may result owing to areas of local shrinking. The vascularity also becomes very irregular. When the coronaries are affected nodular thickenings may be present on the branches on the surface of the heart.

Raynaud's Disease. Although in this disease the essential abnormality is in the nervous system and is characterised by excessive vaso-constriction, it may be conveniently considered here as the effects result from arterial contraction. The disease as described by Raynaud comprises three groups of phenomena, viz. (*a*) local syncope, (*b*) local asphyxia and (*c*) symmetrical gangrene. These phenomena are paroxysmal in origin and peripheral in their distribution, affecting chiefly parts of the extremities. They may occur in the sequence mentioned but this is not always the case ; local asphyxia, for example, may occur without preceding syncope. All the effects appear to be the result of excessive contraction of vessels in different degrees, and in their production cold plays an important part. In fact, the changes in Raynaud's disease may almost be regarded as a perverted exaggeration of the action of cold seen in many normal individuals. Local syncope is evidenced by intense pallor, coldness and disturbance of sensation ; the fingers are frequently affected—the patient suffers from 'dead fingers.' The condition underlying local syncope is evidently contraction of all the vessels of the part. In local asphyxia, which often follows the previous condition, the part becomes livid and of dark colour, somewhat swollen and remaining cold. There is manifestly here contraction of arteries, while the capillaries and veins are dilated and filled with blood of high oxygen unsaturation. When gangrene is going to supervene the cyanotic area becomes deeper in colour, brown or almost black, blisters form and the signs of actual death of the part soon become manifest. The parts most frequently the seat of gangrene are the fingers, toes, ears and tip of nose. It has been repeatedly shown that the gangrene is not the result of thrombus formation in the vessels, the lumen being found on dissection to be patent. It is evidently due to excessive spasmodic contraction of the arteries, depending apparently on a state of hyper-excitability of the vasomotor centre, though the nature and causation of the latter are not known. In view of this fact, operations have been undertaken with the object of eliminating the action of the sympathetic. Peri-arterial sympathectomy was first carried out, but the results on the whole were unsatisfactory. Ganglionectomy (upper cervical or lumbar, as the case may be) has been attended by much more favourable and sometimes striking results, the effect on the vascular condition being produced almost at once and apparently being lasting. Sometimes late in Raynaud's disease structural changes may occur in the arteries, but the results of operative procedure demonstrate clearly an overaction of the sympathetic as the essential factor. It may be added that some of the phenomena seen in Raynaud's disease, such as local asphyxia, may be met with in association with paroxysmal hæmoglobinuria (p. 487).

ANEURYSMS

An aneurysm may be said to be a space or sac formed by the widening or extension of the lumen of an artery, and thus containing blood or clot. A distinction is often drawn between a *true* and a *false* aneurysm. The former is sometimes stated to be one enclosed by the stretched and altered vessel wall; whilst the latter is said to be due to rupture, the blood then being enclosed by the condensed tissues around. This distinction, however, is not quite correct. as in the 'true aneurysm' the characteristic elements in the wall, muscle and elastic tissue, soon disappear, and the blood is enclosed by connective tissue, much of which may be derived from the tissues outside the vessel. If the terms are to be used, a true aneurysm should mean one formed by *slow stretching*, and, it may be, gradual destruction of the artery wall, while a false aneurysm is one produced by *actual rupture* of the wall. After a time the two forms come to be closely similar in essential structure. An aneurysm may involve the wall in its whole circumference, and is then usually of *diffuse* or *fusiform* type; or it may form as a bulging, and then tends to be of the *saccular* type. In the latter, the aperture of communication with the artery may be relatively small or large, and in fact the whole of the wall may be incorporated. These descriptive terms are, however, applicable only to aneurysms in the earlier stages. At a later period they may extend in various directions and become quite irregular in form.

Causation. In the case of every aneurysm the essential cause is some local lesion or weakness of the wall, and this must involve the media. The force which forms an aneurysm is of course the blood pressure, and accordingly aneurysms are commonest in those subjected to the strain of hard physical labour. But high blood pressure never leads to an aneurysm so long as the wall is in a healthy condition. The lesion of the media, which is the most important factor, may result from an extension of disease either (*a*) from outside the vessel, or (*b*) from within, that is, through the intima which is first implicated.

(A) *Extension of disease from outside* is seen in syphilitic mesaortitis, which is by far the commonest cause of aneurysms of the aorta; here, as has been described, the disease begins in the adventitia and passes inwards around the vasa vasorum. The lesion, having reached the media, leads to destruction of the elastic tissue and muscle fibres, and thus to a local weakness.

Aneurysms may arise also by the extension of an ulcerative process to the artery wall, which thus becomes weakened and yields. In such cases the ordinary result is that the intima reacts in the form of endarteritis obliterans, or the vessel may become thrombosed; but when the ulcerative process has proceeded more rapidly, the damage to the media may occur before these defensive processes have had time to come into play. The aneurysms which form in tuberculous cavities in the lungs, are an excellent example of this kind of aneurysm. They are sometimes as large as a cherry, but usually they are smaller, and they may produce a fatal result by rupture. In the case of a gastric ulcer, an arterial branch may become similarly involved, and an aneurysm, which may afterwards rupture, may be produced before the vessel has undergone obliteration. Of the same nature as these aneurysms is the type met with in polyarteritis nodosa (p. 309), where the essential change is necrosis and weakening of the media as the result of an inflammatory process spreading from outside.

(B) *Extension of disease from within* to the media is seen in the case of atheroma. As has been described, damage of the media by this lesion occurs chiefly in the smaller arteries, and atheroma may be present in the aorta in marked degree without seriously affecting the media. Sometimes, however, the media of the aorta may be considerably diseased underneath an atheromatous patch, and Coats considered that a calcified patch when present had an important effect, impinging on and damaging the media. It has come to be recognised, however, since the syphilitic lesions have been more fully differentiated, that atheroma is a relatively uncommon cause. Extension of damage from within, that is, through the intima, is well exemplified in the case of *infective* or *mycotic aneurysms* due to an invasion of pyogenic organisms from an infected thrombus or embolus.

Aneurysms of the Aorta and its Large Branches. The commonest site is the aortic arch, because it is the part most frequently affected by syphilitic disease; next come the thoracic and the abdominal aorta, and then the main branches from the arch. As has been stated above, syphilitic disease is by far the commonest cause of large aneurysms. It will be readily understood from the description given above (p. 302), how the supporting power of the media becomes weakened at places by the syphilitic lesion, and it is not uncommon to find in a syphilitic aorta small aneurysms or depressions in various stages of formation. Ordinary degenerative atheroma is occasionally a cause of localised aneurysm, especially in the abdominal aorta, though it more frequently gives rise to general dilatation of the wall. It is to be noted that the age of most frequent occurrence of aneurysm (40 to 50) is earlier than that at which marked atheroma is common, and this is due mainly to syphilis being the common cause, partly to special physical strain at the earlier period. It is of interest to note that since the introduction of salvarsan treatment aneurysms have become much less frequent.

When a distinct aneurysmal pouch has formed in a large artery, it will usually be found that the muscular and elastic tissues of the media have their continuity broken at the part; in fact there may be little media left even when the pouch is quite small, and any remains of the elastic tissues are in a more or less degenerated condition. The intima disappears in places and ultimately altogether, and thus the wall of the sac before long comes to be composed of layers of fibrous tissue, on which laminated thrombus often forms. Embolism from such a source is rare. Blood infiltrates the wall of an aneurysm and coagulates; and thus the limits of the wall come to be badly defined. Soaking of blood may extend for some distance into the tissues around, and accordingly, when the aneurysm is ulcerating, say into a bronchus, there may be slight hæmorrhage for some time before the final gush occurs.

Once an aneurysm has started it tends to go on increasing in size. This is partly because its wall is weaker than the original vessel wall, and partly because of the principle in physics that as the diameter increases the tension on the wall increases proportionately, the blood pressure remaining constant; that is, the larger the sac the greater is the stretching force to which it is subjected. Occasionally thrombus formation occurs in thick layers which come to fill the whole sac, and thus a spontaneous cure may follow. This, however, is rare, and takes place chiefly when the aperture into the artery is comparatively small; as a rule, the thrombus in its growth does not keep pace with the enlargement of the sac, and only partially fills it. As an aneurysm increases in size, the maximum extension may be in any direction, and accordingly it may be impossible to say during the life of the patient from what part of a vessel, and sometimes even from which vessel, the aneurysm has taken origin.

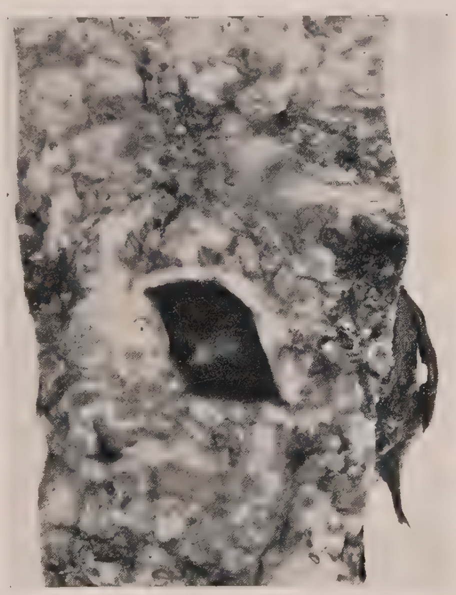

Fig. 207.—Abdominal Aorta, showing Orifice of Aneurysm.

The intima of the aorta is the seat both of atheroma and of syphilitic disease.

Effects. An aneurysm, of course, produces important results by *pressure* on surrounding structures; if these are movable they are displaced, but if they offer resistance they undergo destructive absorption. The most striking example of the latter effect is seen in the case of bone, which often undergoes extensive erosion and destruction. Thus the bodies of the vertebræ may become eroded and the bare bone come to form part of the wall of the sac; the intervertebral discs offer greater resistance to absorption and persist longer. The pressure effects of an intrathoracic aneurysm are very various. The large veins may be pressed on, or thrombosis may follow, and venous engorgement in the corresponding area will result. The œsophagus may be implicated and swallowing may be interfered with; a bronchus may be narrowed and retention pneumonia occur; and in the case of aneurysm of the transverse part of the aortic arch, a common result is involvement of the left recurrent laryngeal nerve with paralysis of the left vocal cord. *Rupture* of an aneurysm may occur into practically any tube or cavity in its neighbourhood, and occasionally takes place externally through the chest wall. The commonest site of rupture is into the trachea or a bronchus, but the sac may burst into the pleura or lung substance, into the pericardium, into the œsophagus, into a large vein, and even into an auricle, the pulmonary artery or the right ventricle. As has been already mentioned, fatal rupture may be preceded by oozing of blood for some time; this is often noteworthy in the case of the respiratory passages.

It is not infrequently stated that aneurysm leads to hypertrophy of the left ventricle. That is certainly not our experience and there does not seem any reason why this result should occur, as there is no interference with the normal output of the heart. Hypertrophy and dilatation may, of course, occur from associated causes; for example, when incompetence of the aortic valve has resulted from spread of the disease from the aorta. But we have seen many cases of very large aneurysms without the presence of any cardiac enlargement.

Aneurysms of the Smaller Arteries, due to chronic disease, such as arterio-sclerosis or atheroma, are relatively uncommon. They are occasionally met with on the splenic, mesenteric, renal arteries, etc. Aneurysm of the popliteal artery, once pretty common according to the published accounts, is now hardly seen. It used to be met with in post-boys and others who had much riding, and its occurrence was favoured by the S-shaped bending which the vessel undergoes when the limb is flexed. Aneurysms of the cerebral arteries have special features, and will be considered by themselves.

Infective or Mycotic Aneurysms. These are produced by invasion of the intima by organisms, usually the pyogenic cocci. This may occur at the beginning of the aorta as the result of *direct extension* of organisms from vegetations in bacterial endocarditis (Fig. 231). The organisms settle on and damage the intima, and an infective thrombus forms. Invasion and weakening of the wall follow, and an *acute aneurysm* is produced, which may rupture; occasionally more aneurysms than one are present. Aneurysm in bacterial endocarditis is not of common occurrence, and according to our experience is met with mainly in staphylococcus infection. In other cases an aneurysm is produced by infective *embolism*, and here also the wall of the artery is weakened by the bacterial action. Such a result is sometimes seen in the cerebral arteries, and fatal hæmorrhage may be produced. An aneurysm of this nature may form also in an artery of a limb or other part of the body.

Cerebral Aneurysms. Aneurysms of the cerebral arteries are of importance as they are comparatively common, and not infrequently rupture and give rise to fatal hæmorrhage. Two varieties may be distinguished, as regards their sites and the period of life at which they occur—viz. miliary aneurysms, and larger aneurysms in connection with the circle of Willis and its branches. *Miliary aneurysms* are often described as the common cause of cerebral hæmorrhage in cases of arterio-sclerosis with high blood pressure. But in our experience they are usually sought for in vain, and many of the little swellings to be noted along the small arterial twigs in such cases are really due to extravasations of blood into the perivascular tissue or into the vessel walls. Such lesions occur especially on the deep nutrient arteries, chiefly in the region of the internal capsule.

Aneurysms of the circle of Willis and its branches usually occur singly, and are often of about the size of a small pea, though sometimes they may be considerably larger (Fig. 208). They are met with in the earlier years of life as well as later, and may form without the presence of any arterial disease. This fact has raised discussion as to their origin. One view, often associated with the name of Kirkes, is that they are due to embolism. He found them especially in cases of vegetative endocarditis, and supposed that an embolus injured the vessel wall mechanically and caused it to yield. Such aneurysms do occur in cases of endocarditis, but are relatively rare; in our experience they are then commonest in connection with the middle cerebrals, which are the most frequent site of embolic plugging. It is likely that in such cases the injury to the vessel wall is really the result of the action of organisms present in the embolus. But in most cases of such aneurysms there is no discoverable source of embolism, and moreover the aneurysms occur practically anywhere, even in situations where an embolus is unlikely to be arrested. For example, in several cases observed by us the aneurysm was on the anterior communicating artery (Fig. 209). In view of the frequent absence of any discoverable cause for such aneurysms, it seems probable that they may be due to some congenital weakness or deficiency of the artery wall. Such an occurrence, of course, cannot be demonstrated after the aneurysm has formed, but recent observations have shown the presence of a deficiency in muscle in

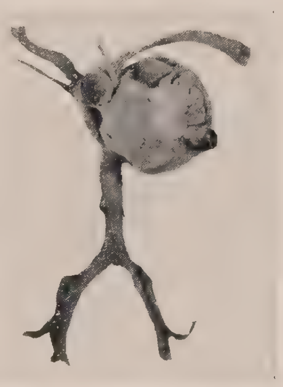
Fig. 208.—Large Aneurysm of Basilar Artery.

other parts of the arteries at the base of the brain when an aneurysm has been present. The deficiency occurs especially in the acute angle between two large branches. An inherent defect in the elastica has not been similarly demonstrated, but there is no doubt that when dilatation starts the elastica soon becomes degenerate. Aneurysms of this type are now often known as *congenital aneurysms.* Occasionally aneurysms of the larger cerebral arteries are due to atheroma. The origin of some of them has also been ascribed to syphilis, and this possibility cannot be excluded. I have, however, never seen an undoubted example of such an occurrence.

Other forms of aneurysm may be mentioned. A *traumatic aneurysm* may be produced by injury to the vessel wall by a stab or bullet wound, or by a spicule of fractured bone. The result is, of course, hæmorrhage into the tissues with formation of a localised hæmatoma, but after a time reactive changes occur around the blood and a layer of granulation tissue is formed, which may produce a remarkably defined wall to the space. Or a vein may be injured at the same time as the artery, in which case the arterial blood makes its way into the vein and causes a pulsatile distension of the latter. Such a condition, which was not uncommon at the elbow in days of venesection, is called *aneurysmal varix.* In other cases again, an aneurysm may effect communication with a vein and then the term *varicose aneurysm* is used. When the vein involved is of large size, for example, one of the large veins of the thorax in a case of aortic aneurysm, serious disturbance of the circulation may be brought about and a fatal result may follow.

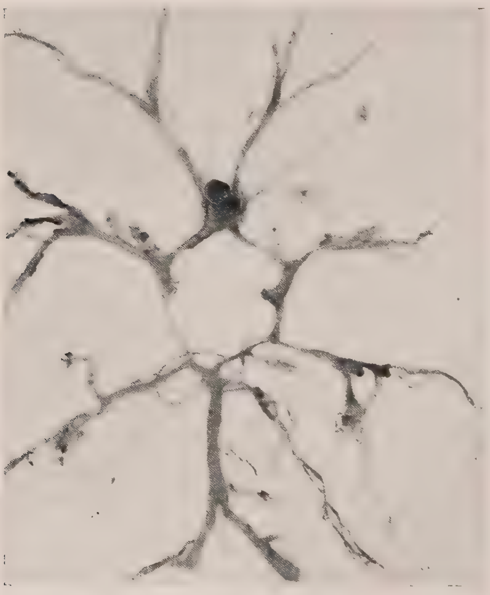

Fig. 209.—Circle of Willis, showing small Aneurysm on the Anterior Communicating Artery.

The term *dissecting aneurysm* is applied when the space containing the blood is actually in the wall of the artery, usually the aorta. The common cause of the condition is some lesion of the media, and the media ruptures before the intima gives way

(Shennan [1]). The changes in the media vary but they are of a degenerative type, often hyaline fibroid or mucoid in character, and are associated with local atrophy and disappearance of muscle and elastic fibres. Such changes, which may be widespread, are ascribed to toxic action but its nature is not known. It is generally agreed that syphilis has no relation to the occurrence of dissecting aneurysm. A less frequent occurrence is that an ulcerated atheromatous patch first gives way and then the blood passes into the media. In either mode of occurrence the blood spreads in the substance of the media rather nearer its outer than its inner margin; the media is thus split up into two layers, hence the term ‘dissecting.’ This process may extend for a considerable distance and the blood may then rupture back into the lumen of the aorta. In this way, the blood flows through a new channel and the upper aperture may be in the arch, whilst the lower is towards the termination of the abdominal aorta. When the condition lasts for a long time, proliferation occurs in the walls of the channel and an appearance simulating new intima may be produced. This is well seen in a specimen which we have, where the upper opening is above a congenital stenosis at the end of the arch. Occasionally, though rarely, a dissecting aneurysm remains localised (Fig. 210). Dissecting aneurysm is commonest in the later years of adult life though it is met with also at an earlier period. High blood pressure with hypertrophy of the heart has been found in the majority of cases. The start of the aneurysm is marked in some cases by sudden lacerating pain. Small dissecting aneurysms usually localised as hæmatomata may form in connection with the smaller arteries—for example, the deep nutrient arteries of the brain, notably in cases of high blood pressure.

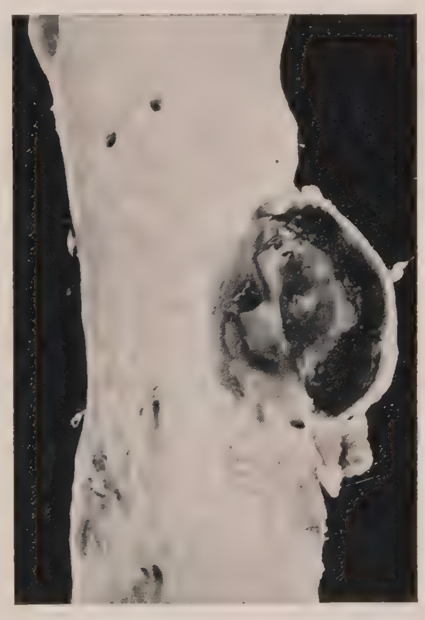

Fig. 210.—Localised chronic dissecting aneurysm; the space in the media is filled with dense clot.

In connection with this subject, we may mention that sometimes there is spontaneous *rupture of the aorta*, apart from the presence of an ordinary aneurysm, and at the site a transverse tear, which may be almost like a cut, is found. The rupture is usually attended by a certain degree of dissecting aneurysm and, in fact, is produced in the same way as the latter, the case appearing as one of ‘ rupture ’ when blood escapes through the aortic wall and causes rapid death. Similar fibroid and mucinoid changes are found in the media, and the intima may be comparatively healthy. Sometimes there are small areas of necrosis with a certain amount of softening, and the term *medionecrosis* of the aorta has been applied. The commonest site of rupture is the arch, often just above the aortic valve and the blood may escape into the pericardial sac (Fig. 211). Rupture of the aorta may be the result of damage to its wall from outside, e.g. by the perforation of an impacted fish bone in the œsophagus, cancerous invasion, etc. It may also be due to very severe injury, for example, that resulting from a fall from a great height.

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[1] A full account will be found in *Dissecting Aneurysms*, by T. Shennan, Med. Res. Council Reports, London, 1934.

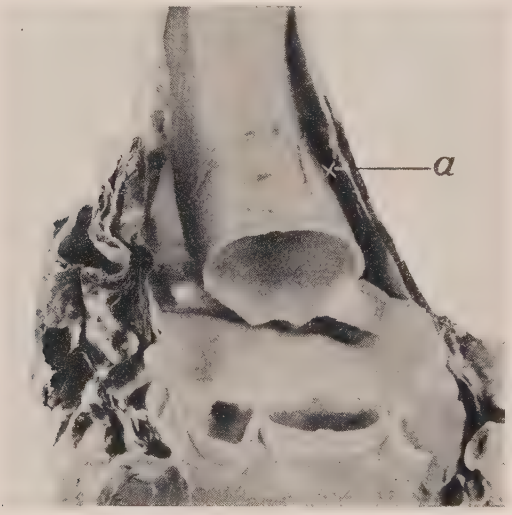

Fig. 211.—Rupture of Aorta with Acute Dissecting Aneurysm.

There is a transverse rupture above the aortic valve and the blood has separated intima and inner part of media almost as a complete tube. *a* points to dissecting aneurysm in which some blood is still present.

The term *cirsoid* or *racemose aneurysm* is applied to a collection of tortuous and dilated arteries which form a pulsatile swelling. The commonest site is the scalp, and a certain amount of atrophy of the underlying bone may be produced. The capillaries and veins of the part may also be increased in number, and the condition is apparently of congenital origin.

(B) VEINS

Compensatory enlargement of the veins, or what is really hypertrophy, takes place, as in the arterial system, when an increased collateral flow is produced by obstruction in a large vein. Here too as in the case of arteries, the dilatation is followed by hyperplasia of the various elements in the wall of the vessels. Veins are, of course, not exposed to the marked variations of blood pressure which occur in arteries, but when they are subject to chronic over-distension, compensatory changes occur in their walls. There is little or no hyperplasia of the muscle, but considerable increase of the elastic tissue occurs, and at a later stage, just as in arteries, this undergoes degeneration, whilst the fibrous tissue becomes thickened and hyaline in appearance. Localised patches of thickening in the intima of veins are not uncommon, but the fatty changes which are so prominent a feature in arteries, are not met with to any extent.

Acute Phlebitis. This condition, which is the result of bacterial invasion, is of great importance in view of the thrombosis which occurs along with it, and the suppurative softening which may follow in the thrombus and give rise to pyæmia. Acute phlebitis is met with in puerperal and other septic conditions, in specific fevers, especially typhoid, etc. In such cases the inflammatory lesion of the wall of the vein may be comparatively slight and then the most prominent feature is thrombosis. In others again, the intima is covered by fibrinous and purulent exudate, and a varying degree of suppurative softening of the thrombus is present.

(*a*) In one type of case, the organisms reach the vein by the circulating blood, settle in the intima, and produce an acute endophlebitis with thrombosis. The inflammation may extend through the wall of the vein and may lead to an accompanying lymphangitis. Such an occurrence is common in the veins of the leg and is attended by pain and tenderness, and, if the vein is large, by œdema of the leg. A portion of the thrombus may be detached and lead to embolism of the pulmonary artery, sometimes with fatal result. Whilst we have said that acute phlebitis is produced by organismal invasion, it must be recognised that all degrees of inflammatory reaction are met with, and it is not always possible to draw the line between the milder forms of infection and simple thrombosis without the presence of organisms. When inflammatory change is slight the chief results are of a mechanical nature due to the thrombosis; these have been described in a previous chapter (p. 21).

(*b*) In the second type of case, the phlebitis is produced by an extension of the organisms from a septic focus outside. The wall of the vein becomes intensely inflamed and often infiltrated with pus, while the intima becomes covered by exudate; this secondary implication of the intima of course again leads to thrombosis. The thrombus formed is at first of the ordinary type, but may become invaded by organisms which produce a purulent softening, sometimes attended by putrefactive change. Pyæmia may result, though this is often prevented by extension of the thrombus beyond the parts invaded by organisms. Such a type of phlebitis is specially apt to occur in certain situations—for example, in the veins of the diploe or cerebral sinuses in middle ear disease, in branches of the portal vein in ulcerative lesions of the alimentary canal, appendicitis, etc., in the uterine veins in septic conditions of the uterine cavity, in the veins of the bone-marrow in suppurative osteomyelitis, and occasionally in the pulmonary veins in cases of bronchiectasis or gangrene of the lungs. It was by such an implication of the veins that pyæmia occurred commonly in connection with wounds in pre-antiseptic days (see also p. 183). In some cases the inflammatory process which has started in a small branch, ascends in the vein and leads to progressive thrombosis and suppuration. This is well seen, for example, in the case of the portal vein, and the condition, known as *pylephlebitis suppurativa*, may lead to abscesses in the liver (p. 609).

Chronic Phlebitis. Chronic inflammatory processes may spread to the walls of the veins and lead to reactive thickening ; in fact, the minute veins are affected in this way in all chronic inflammatory conditions. Such a condition can often be well seen in syphilitic lesions, especially in the smaller venous branches, both in the primary and later stages. In cases of nodular gummatous periarteritis (p. 304), nodules of character similar to those on the arteries have been observed along the veins. Chronic phlebitis is occasionally met with in the large vessels and the cause may be quite obscure. It is seen, for example, in the portal vein, where it may occur apart from syphilis. Chronic phlebitis may, of course, lead to thrombosis, and when this has existed for some time, it may be impossible to say whether the changes present in the vein wall are primary in nature or secondary to the thrombosis.

Tuberculous invasion of veins, which is of great importance in relation to acute miliary tuberculosis (p. 98), is seen in two forms. In one, where infection apparently takes place from the blood, there is an affection of the intima, in which single or multiple foci may occur. Occasionally the lesion is of the nature of a raised yellowish patch of considerable extent and thickness, and when it ulcerates, numerous bacilli pass into the blood stream, acute miliary tuberculosis resulting. This lesion has been met with most frequently in the veins of the lungs, but occasionally in other parts. In the other mode of blood infection a caseous mass, often in a lymphatic gland, invades and destroys the wall of the vein and, on its erosion, a similar result follows.

Veins may be invaded by *malignant tumours*, and a growth may occasionally extend in the lumen for some distance. This is sometimes a prominent feature in cases of hypernephroma of the kidney; the tumour growth is often attended by thrombosis.

Varicosity of Veins. Dilatation of veins, accompanied by lengthening and varicosity, may affect a group in a diffuse manner, or may be more in the form of saccular dilatations. Certain veins are specially prone to be affected—the veins of the legs, notably the long saphenous vein; the spermatic veins, especially on the left side; the pampiniform plexus, and in portal obstruction the hæmorrhoidal and lower œsophageal veins (p. 22). In some cases the condition may be clearly traced to over-distension by some obstructive lesion, but in other instances, e.g. in varicocele and in varicose veins of the legs, it is sometimes not possible to state its exact cause. Distension of a vein such as the saphena may lead to incompetence of valves, and thus greater hydrostatic pressure, owing to the increased column of blood, acts on the wall and increases the dilatation; in this way a vicious circle becomes established. In varicose veins, atrophy of the muscle and elastic tissue occurs and the walls become composed chiefly of fibrous tissue. Occasionally, saccular dilatations come to communicate with one another. Signs of irritation are often present in the connective tissue outside, and thus thickening and adhesion result. The nutrition of the skin over varicose veins of the legs may become interfered with and an eczematous pigmented condition be produced. Indolent ulceration of the skin not infrequently follows, and may occasionally lead to severe hæmorrhage from the dilated vessels. Thrombosis also is apt to take place in a varicose vein; the thrombus may be imperfectly organised owing to the fibrous state of the vessel wall and may become the seat of calcification (p. 171). A common site of phleboliths is the pelvic veins, and their shadows are sometimes seen in X-ray photographs.

(C) LYMPHATIC VESSELS[1]

The view now generally accepted is that the lymphatic vessels form a closed system separated by an endothelial layer from the tissue spaces. The separation, however, is very easily broken. Thus not only do organisms, leucocytes and tumour cells, readily pass into the lymphatic vessels, as can easily be understood, but also red corpuscles which escape from the capillaries in inflammation follow the same path and may be present in considerable number in the lymphatics draining an inflamed area. We may thus regard the lymphatic vessels as affording an easy means of communication between the tissues and lymphatic glands, and any morbid process in the former may readily be transferred to the latter. Involvement of the lymphatic glands in this way occurs in two main conditions, namely (*a*) infections and (*b*) tumours, especially carcinoma. In both of these the extension may be due to metastases in the strict sense, that is, to convection of the organism or tumour cell by the lymph stream, or else there may be a progressive involvement of the lymphatic vessels by the morbid process, which afterwards reaches the glands. This latter occurrence in the case of infections is evidenced by a lymphangitis which may be either acute or chronic, while in the case of tumours the growth of the cells takes place within the lymphatics, leading to what is practically an injection of them (p. 236).

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[1] For details, see *Lymphatics, Lymph and Tissue Fluid*, by C. K. Drinker and M. E. Field. London. 1933.

Acute Lymphangitis. In the course of the spread of organisms along the lymphatics, inflammatory changes may be set up in the walls. This is seen, for instance, in the case of poisoned wounds, in erysipelas and in phlegmonous conditions, especially in those produced by streptococci. Along the lymphatics of the part, redness, swelling and tenderness are present, these indicating the spread of the inflammatory condition. Spreading lymphangitis is an important feature in connection with septic inflammations of the uterus and may be followed by suppuration, especially in the loose cellular tissue of the parametrium. In other cases of bacterial infection, the organisms are frequently carried by the lymphatic vessels without settling in their walls and giving rise to inflammatory change on their way. Thus inflammation of the axillary lymphatic glands may result from a poisoned wound on the hand, without the occurrence of spreading lymphangitis. A similar striking example is seen in plague, where even at the site of infection there is usually no inflammatory reaction, the first lesion appearing in the related lymphatic glands.

Chronic Lymphangitis occurs in a variety of conditions and is an important feature in many types of chronic interstitial inflammation. A striking example of non-infective lymphangitis is seen in silicosis of the lungs, where fine stone particles which have reached the lymphatics from the alveoli are carried in various directions and lead to a fibrosis of the pulmonary tissue (p. 411). In various chronic infections the spread of organisms by the lymphatics is of high importance. This is well illustrated in the case of *tuberculosis*, in the early stages of which the disease may be regarded as essentially one of the lymphatic system. Here again, the organisms may be carried to lymphatic glands without causing lesions on their way; but, on the other hand, they may settle in the walls of the lymphatic vessels and give rise to tubercles which thus come to form rows along the vessels. A common example is in connection with a tuberculous ulcer of the intestine, where small tubercles may be found along the lymphatics passing from the floor of the ulcer, and also in their further course in the mesentery. The thoracic duct may become involved by spread of bacilli among the lymph stream. Ulceration of lesions produced in it may set free a large number of tubercle bacilli which may be carried to the blood stream and set up acute miliary tuberculosis (p. 98).

In *syphilis* also, chronic lymphangitis is a prominent feature.

This is the case in connection with the primary lesion, and fine lines of induration occur along the lines of the lymphatics leading from it. The change is a chronic inflammatory one due to the spread of the spirochætes by the lymph stream, and is characterised by proliferation of the lining endothelium as well as of the connective tissue cells in the walls of the vessels. The organism of syphilis has a predilection for perivascular lymphatics, and the serious results caused in the aorta are due to this mode of spread, as has already been described (p. 102).

Lymphatic Obstruction. When the large lymphatics become obstructed, an enlargement of the anastomotic channels occurs just as in the case of the veins, and considerable varicosity may result. The most striking examples of such effects are seen in filarial disease, as will be described below. It will also be explained how obstruction of the lymphatic vessels along with the results of inflammatory attacks may give rise to irregular thickening and induration of the tissues, resulting in the condition known as *elephantiasis*. This form of lesion may, however, occur apart from filarial infection, and is sometimes seen as the result of repeated attacks of erysipelas, which appear to obliterate many of the small lymphatics and at the same time cause overgrowth of the connective tissue. Obstruction of the thoracic duct, sometimes due to a chronic tuberculous lesion, may be followed by rupture of some of the dilated abdominal lymphatics and thus chylous ascites results ; such obstruction is not uncommon in filarial disease.

The relation of the lymphatic system to the spread of cancer and other forms of malignant growth has already been described (p. 235).

Filarial Disease. Of the genus *Filaria* several species are found in the tissues of the human subject, and some of them produce embryos or microfilariæ which inhabit the blood. The term *Filaria sanguinis hominis* is applied in a general way to such microfilariæ, and these may belong to at least four species of filariæ, which are distinguishable by morphological and other characters. The presence of such a microfilaria in the blood may be characterised by periodicity ; for example, it may appear at night—*Microfilaria nocturna*, or during the day—*Microfilaria diurna*. Again, the parasite may be constantly present in the blood—*Microfilaria perstans*, of which there are two species. The most important of these filariæ is the *Filaria bancrofti*, the embryo of which is the *Microfilaria nocturna*. We shall give an account of this parasite and the important effects produced by it.

Filaria bancrofti. The parasite has a widespread distribution in tropical and sub-tropical countries, and in certain places more than a quarter of the population may be infested (Manson) ; as stated above, its embryo is the *Microfilaria nocturna*. The adult worms, male and female, are thin filiform organisms, little thicker than coarse hairs ; they are of whitish colour and show wriggling movements. The female is about three inches in length, whilst the male is shorter and rather thinner and has a spirally twisted tail. Several worms often occur together coiled up in a bunch, especially within the thoracic duct or in large lymphatic vessels, commonly in the pelvis or groins. The females are viviparous and produce small embryos or microfilariæ, which pass by the lymphatics to the bloodstream, where they are readily found on microscopic examination. The microfilariæ measure about 0·3 mm. in length and their thickness is about equal to the diameter of a red corpuscle (Fig. 212). The body is everywhere enclosed in a loose sheath within which the little worm may be seen to move backwards and forwards. This sheath represents the shell of the ovum or vitelline membrane. The head bears a hemispherical proboscis, which has a small protrusible spine and is covered by a retractile six-lipped prepuce. Only rudiments of organs are present, and near the cephalic end there is a V-shaped spot. The microfilariæ, which apparently produce no harm, appear in the blood in the evening, and they can be easily detected microscopically by means of their movements. During the daytime they disappear from the peripheral circulation and collect in the blood vessels of the lungs. The intermediate host is a female mosquito, usually of the culex genus, which becomes infected by swallowing the blood containing the microfilariæ. Within the stomach they escape from their sheaths and pass to the muscles of the insect. Within these they undergo further development, and thereafter pass to the labium, where they are in a position to gain access to the human tissues when the insect bites.

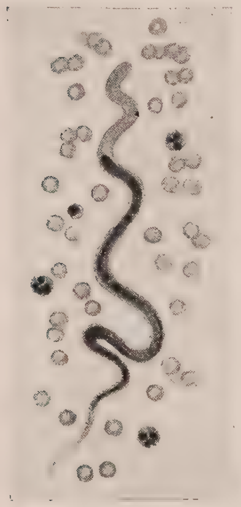

Fig. 212.—Microfilaria nocturna (embryo of Filaria bancrofti) in Human Blood. (Rd.M.) × 300.

So far as the human subject is concerned the chief effects are produced by the adult worms. The presence of the masses of the adult worms in the lymphatics has a twofold effect, namely, (*a*) the causation of obstruction and (*b*) the production of a certain amount of irritation and damage to the walls of the lymphatics, which often results in their permanent closure. When the thoracic duct is obstructed, it becomes dilated below, and there is also a great varicose enlargement of the lymphatics drained by it, which may form large masses in the abdominal cavity. There is a development of the anastomoses with the lymphatics of the abdominal walls, etc., and these also become varicose. Thus the scrotum may be the seat of this change and become greatly swollen, *lymph scrotum* resulting; and in a similar way swellings may form in the groins—known as *varicose inguinal glands*. These lesions are, however, only the outlying manifestations of the general lymphatic varicosity. The dilated lymphatics contain chyle which is passing off by the collateral channels, and when rupture occurs a milky fluid escapes. The fluid contains fatty globules, red corpuscles in varying number, and sometimes microfilariæ. When rupture takes place into the peritoneal cavity *chylous ascites* is produced; when it occurs in the kidneys or bladder *chyluria* results.

Another important result of filarial infection is the production of a form of elephantiasis—*elephantiasis Arabum*—which is of common occurrence in regions where filarial disease abounds. The condition usually starts with an attack of erysipelatoid inflammation and lymphangitis, and is intensified by subsequent attacks. The skin and subcutaneous tissues thus undergo marked thickening and swelling ; the part affected becomes greatly enlarged and the skin and other tissues become indurated, irregularly folded or nodulated, hence the name applied to the condition. In the vast majority of cases, more than 90 per cent., a lower limb is the part affected ; less commonly other parts, such as the scrotum, mamma, or an upper limb, are involved. When the affection is of long standing, the leg may reach an enormous size, while a scrotal tumour may weigh 30 lbs., or even more. According to Manson, elephantiasis occurs when the lymphatic vessels become completely obstructed and secondary inflammatory change follows. He found in some cases that the ova of the parasite had been set free instead of the living embryos, and pointed out that such ova, apparently expelled by a process of abortion, would, owing to their breadth as compared with that of the living microfilariæ, be very effective in causing obstruction. Irritation also would be produced and secondary thickening of connective tissue would follow ; and this would be accentuated by attacks of erysipelatoid inflammations, which are fairly common. In cases of elephantiasis, as a rule microfilariæ are not to be found in the blood, and Manson considered this to be due to complete obstruction of the lymphatics, or in some cases to the actual death of the female parasites.

CHAPTER IX

CIRCULATORY SYSTEM

II. THE HEART

Lesions of the heart and their results may be conveniently studied as affecting (*a*) the myocardium, (*b*) the valvular apparatus, and (*c*) the conducting system. It must, however, be recognised that so far as pathological effects are concerned these different parts of the heart are closely interdependent. An affection of one part may implicate one of the others, or again, the same disease may affect two or even all three together. Thus the lesions of the valves have important and often serious effects on the heart muscle, and, conversely, disease of the myocardium may lead to incompetence of the mitral and tricuspid valves ; again, such a disease as syphilis or acute rheumatism may produce definite lesions in the myocardium, in a valve or valves, and in the auriculo-ventricular bundle. The pathological picture may thus be of considerable complexity, and it is of great importance that the student should be familiar not only with the nature of each lesion and its common effects, but also with the various lesions to which a given disease may lead.

It may be of assistance to state at this stage that the main causes of serious cardiac disease are (*a*) *rheumatism,* (*b*) *bacterial infection of the valves,* (*c*) *diseases of the coronary arteries and* (*d*) *syphilis.* Both gradual heart failure and sudden death are usually due to one or other of these affections.

I. LESIONS OF THE MYOCARDIUM

The chief causes of these are :—

(*a*) General conditions of malnutrition.

(*b*) The action of toxins in fevers and infections.

(*c*) The actual invasion of the cardiac muscle by organisms, e.g. the organism of rheumatism, the pyogenic organisms, spirochæte of syphilis, etc.

(*d*) Lesions of the coronary arteries, which produce a very important group of structural alterations in the cardiac muscle.

To speak generally, the effect of such lesions is to reduce the efficiency of the cardiac muscle, and serious symptoms may thus result ; but it must be borne in mind that a healthy heart has a very large margin of reserve power, and hence the effect of a lesion may not become apparent until some undue strain is put upon it. Hence it is of importance to recognise the diminution of reserve power which accompanies such lesions.

Degenerative Changes

Brown Atrophy. This, as the term implies, means a wasting of the cardiac muscle, attended by a brown appearance. It occurs in varying degree in all chronic wasting diseases with great emaciation, e.g. carcinoma, tuberculosis, etc. ; marked examples are met with also in Addison's disease, probably as the result of the low blood pressure which is present. In extreme examples the weight of the heart may be reduced almost to half the normal. In typical examples the cardiac muscle is of a deep brown colour, often dry and somewhat friable. The epicardial fat in most cases has largely disappeared, and is sometimes replaced by an œdematous tissue of mucoid appearance, while, owing to the wasting of the heart, the superficial arteries are tortuous and prominent. The apices of the papillary muscles are often somewhat fibrous, and there may be increased opacity of the endocardium generally. Microscopic examination shows that there is simply a diminution in size of the muscle fibres, the fibrillæ being well preserved, while there is a marked increase of the granules of brownish pigment, which are present at the poles of the nucleus in all adults. The condition may thus be regarded as corresponding to an exaggerated senile change. The granules are of lipoid nature (p. 168).

Another variety of atrophy is the *ischæmic atrophy*, which results when the muscle has its blood supply interfered with, but not to a degree sufficient to kill the muscle. It is seen especially in arterial disease. Here the chief change is a gradual disappearance of the contractile fibrils, and the muscle cells come to have an empty appearance. When an infarction involving the inner part of the heart wall occurs, there are often to be seen under the endocardium several rows of cells which have escaped necrosis, these being able to obtain nourishment through the endocardium from the blood in the cavity. The outermost of them, that is the cells farthest from the endocardium, usually show varying degrees of ischæmic atrophy.

A form of pigmentation of rare occurrence is due to the deposit of hæmosiderin in the muscle fibres. This is met with in cases of hæmochromatosis (p. 166), which may be attended by bronzed diabetes. The hæmosiderin is deposited in lines in the long axis of the muscle fibres, and is sometimes present in considerable amount. It gives the characteristic iron reaction.

Cloudy Swelling. In acute infective conditions the myocardium is frequently injured, and the damage may be either general or focal in character. Cloudy swelling is a general change produced by toxic action, especially when long continued. Its importance has probably been exaggerated, although, after infective fevers, septicæmias, etc., it is common to find the heart in a condition corresponding to the description generally given. The most striking examples of the condition are met with in typhoid fever where there has been long-continued pyrexia, and sometimes in septicæmia. The heart muscle may be said to be softer and rather paler than the normal, especially in the inner part, and usually of a pinkish colour; it is often rather friable to the touch. On microscopic examination the usual changes are found (p. 140). Cloudy swelling is often followed by fatty degeneration, less frequently by actual necrosis of the muscle cells. There can be little doubt that cloudy swelling may occur in infections and recovery thereafter take place.

Fatty Infiltration. This simply means an increase of the adipose tissue of the epicardium both in thickness and extent, and an ingrowth of it into the cardiac muscle; it thus occurs chiefly where normally the fat is most abundant. It affects especially the right ventricle, and on section of the wall the layer of fat is seen to be increased in thickness, and the muscle is infiltrated and sometimes largely replaced by fat. In extreme cases the fat appears underneath the endocardium in the form of streaky yellow patches of adipose tissue, running in the lines of the columnæ carneæ. This is more commonly seen in the right ventricle, but is occasionally met with in the left also. As the adipose tissue increases in amount, many of the muscle fibres undergo atrophy and disappear, and the surviving muscle is in thin strands separated by fat (Fig. 213); many of the muscle fibres in the neighbourhood of the fat cells may show fatty degeneration. For these reasons, in extreme cases the working power of the heart is interfered with, dilatation is apt to follow, and occasionally even rupture may occur (Fig. 214). Fatty infiltration may be regarded as an accompaniment of general adiposity, but is not always in direct proportion to this; in fact, in some cases it may be extreme where the increase of fat throughout the body is not very great. In such cases its cause is obscure.

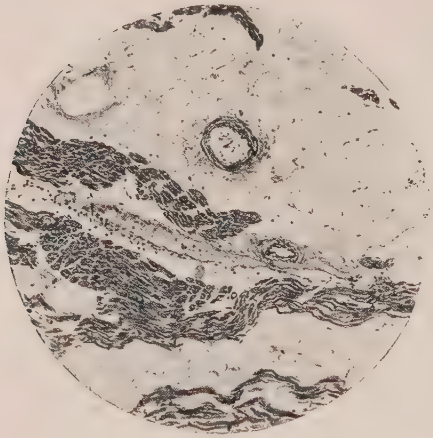

Fig. 213.—Fatty Infiltration (lipomatosis) of Heart Muscle, showing infiltration of Fat Cells around Blood Vessels and between Muscle Fibres, the latter becoming atrophied. × 60.

Fatty Degeneration. In this condition fat occurs in the form of minute globules within the muscle fibres of the heart. The globules are in longitudinal rows, and even when they are very abundant, the fibrillæ may still be visible (Fig. 88); but it cannot be doubted that the change must impair the working power of the muscle. The condition is, of course, to be distinguished from fatty infiltration. Fatty degeneration is met with in severe anæmic conditions—pernicious anæmia, leukæmia, etc., and is produced also by bacterial and other poisonings. It is common as the result of septic conditions, being preceded by cloudy swelling, and it is usually a marked feature in chloroform and phosphorus poisoning; it is met with also in diabetes, but its occurrence in that disease is variable. Some fatty degeneration, irregular in distribution, may occur as a result of disease of the coronary arteries, but it is usually not a prominent feature; fibrosis is the all-important result.

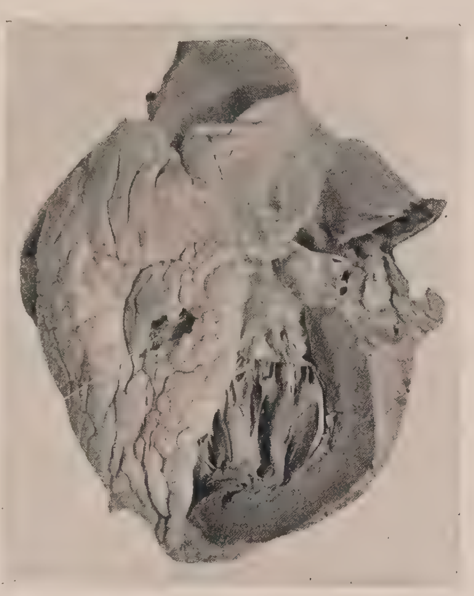

Fig. 214.—Extreme Fatty Infiltration of Heart in front of Right Ventricle.

A is an aperture where spontaneous rupture took place.

While fatty degeneration may affect all the chambers, it is usually most marked in the left ventricle; but occasionally in cases of obstruction to the pulmonary circulation, e.g. in emphysema or fibrosis of the lungs, the right ventricle mainly is affected. In anæmic conditions the degeneration is chiefly in the areas farthest from the arteries, that is, it is pararterial in distribution, and thus the distribution is distinctly patchy (Fig. 215). In such a case, the myocardium is pale with a tendency to yellowish tint, especially in the inner part, while underneath the endocardium are to be seen small flecks or patches of more distinctly yellow colour. These are often most marked over the papillary muscles, where they are arranged as transverse markings, resulting in the so-called ‘thrush-breast’ appearance. Such an appearance is quite characteristic of fatty degeneration, but when it is absent it may be difficult or impossible to make a definite diagnosis. The fatty degeneration which occurs as the result of poisons, long-standing sepsis, etc., is usually more or less diffuse in distribution, and mottling is little in evidence. In the infections it is rarely so marked as to admit of recognition by the naked eye, but in phosphorus and chloroform poisoning it may be extreme and unmistakable. The importance of fatty degeneration as a cause of sudden death has, we think, been much exaggerated. It must be admitted that the reserve power is diminished and the heart may suddenly fail, but in cases of sudden death some other cause, such as fibrosis, disease of the coronary arteries, or general cardiac dilatation, is usually to be found. The nature of fatty degeneration has already been discussed (p. 146).

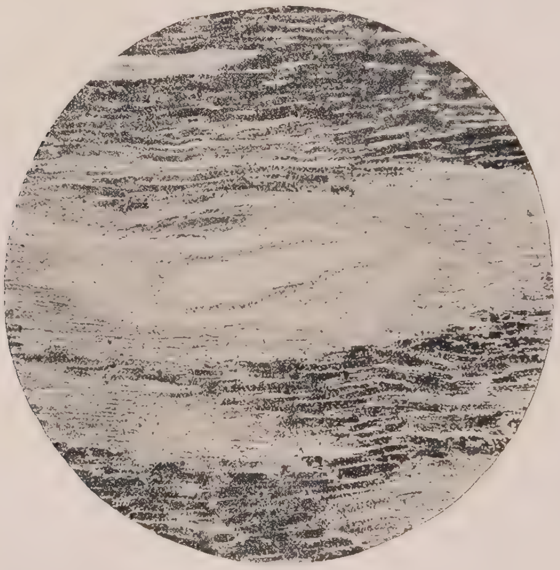

Fig. 215.—Fatty Degeneration of Myocardium in a case of Pernicious Anæmia, showing pararterial distribution (stained with osmic acid). (Cowan and Ritchie).[1] × 200.

Calcification. As will be described below, calcification is a common occurrence in indurated valves in chronic endocarditis; and in some cases of chronic pericarditis, often tuberculous, there may be considerable deposit of lime salts. In the substance of the heart muscle a similar process may occur in old fibrous bands, gummata, etc., but in addition to this there may be deposit of lime salts in the *muscle fibres*, sometimes in the form of a diffuse impregnation, sometimes as fine granules (Coats). Cases of such a nature are, however, rare. In some instances the condition seems to be a sequel to necrotic change; in others the etiology is quite obscure.

Segmentation and Fragmentation of the Myocardium. The former term is applied to a separation or dissociation of the muscle cells at the cement line of junction; the latter to a transverse fissuring of the fibres (Fig. 216). Both conditions may be present together, but fragmentation appears to be the more common. These changes are not infrequently met with in atrophied

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[1] The following figures are reproduced from *Diseases of the Heart*, 3rd. edit. London, 1935, by John Cowan and W. T. Ritchie, by kind permission of the authors:—Figs. 215, 222, 239, 240, 241, 243, 244.

and degenerated hearts, and occur especially in the papillary muscles; they are said to be found only in adult life. Fragmentation and segmentation have been observed in the hearts of healthy individuals in cases of violent death, e.g. by hanging, strychnine poisoning, etc., and they have been produced experimentally in animals by similar conditions. It seems pretty clear that they represent a lesion occurring in the death agony. They are generally supposed to be the result of strong irregular contraction of the muscle fibres, and it is quite intelligible that the dissociation and rupture are more likely to occur in degenerated hearts. The view once put forward that they represent a real lesion of importance in relation to cardiac failure, is now regarded as quite untenable.

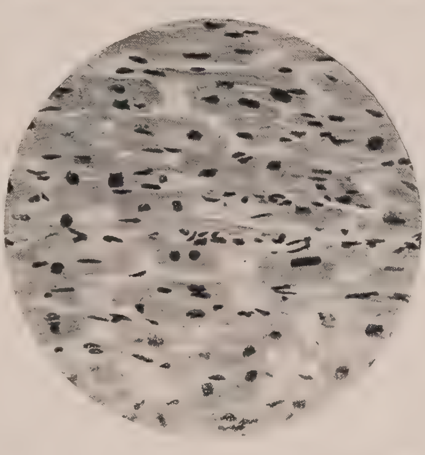
Fig. 216.—Segmentation and Fragmentation of Heart Muscle. × 250.

Inflammatory Changes

Acute Myocarditis. If we except the cases where organisms are actually present in the muscle, this condition may be said to be badly defined. Acute myocarditis may be due to extension of inflammation from the region of the valves or from the pericardium, but when it is primarily in the muscle, it is always *focal* in character; there is no such lesion as a general acute inflammation of the muscle. In some cases, notably in diphtheria, the lesion is really one of *focal necrosis* of muscle cells, produced by the direct action of toxins, though this is followed by reaction in the tissue around. In others, especially in acute rheumatism, inflammatory foci form around the blood vessels, and the adjacent muscle also suffers and is in part destroyed. A *parenchymatous* and an *interstitial* form are accordingly sometimes distinguished, but the ultimate results are pretty much the same in both, and the lesions merely indicate the predominant change at an early stage. A more important distinction depends on the presence or absence of organisms. Thus the changes in the myocardium may be simply a toxic effect as in diphtheria, or may be due to the actual presence of organisms as in acute rheumatism and pyogenic infections —*toxic* and *infective myocarditis* respectively.

In *diphtheria*, as has been mentioned, and to a less extent in scarlet fever, influenza, typhoid and various other infections, numerous small areas of hyaline change may be found in the muscle, on microscopic examination. The affected fibres have become swollen and glassy in appearance and have lost their nuclei, the condition in fact corresponding to coagulation necrosis, whilst around them there is leucocyte infiltration; most of the cells are mononuclears and lymphocytes, but polymorpho-nuclear cells also may be present. In some cases of diphtheria a lesion of this kind, attended by much leucocytic infiltration, has been found to be present in the auriculo-ventricular bundle, and to have caused acute heart-block (Fig. 217). The necrosed fibres afterwards undergo absorption, whilst the connective tissue cells in the areas of infiltration undergo a certain amount of proliferation; hence small fibrous patches ultimately result. Such acute lesions do not, as a rule, produce any change recognisable by the naked eye, although sometimes the myocardium shows pale areas which may suggest the existence of the condition.

Rheumatic Lesions. It is now recognised that acute rheumatism is characterised by the occurrence of focal lesions in various parts of the body, such lesions being associated with and partly leading to the more diffuse inflammatory changes which have been for long recognised as features of the disease. Such focal lesions occur especially in the heart, in the capsules of joints, subcutaneous tissue, walls of blood vessels, etc. In the myocardium they are frequently met with; endocarditis, which is of common occurrence, and also pericarditis, are secondary to their presence. In the myocardium they occur as small nodules which may be just visible to the naked eye and are often described as submiliary, though they are usually discoverable only on microscopic examination. They may be met with in any part of the heart, but are more common on the left side, both in the ventricle and in the auricle, and are more common in the inner part of the myocardium; they also occur in the substance of the valves. These minute rheumatic nodules are now usually known as 'Aschoff bodies' (Figs. 218, 219). On microscopic examination of a fully developed example, the centre usually shows a varying amount of hyaline necrosis which is surrounded by a reactive zone of endothelioid cells and leucocytes. A nodule often contains one or more cells of the giant-cell type, though these are relatively

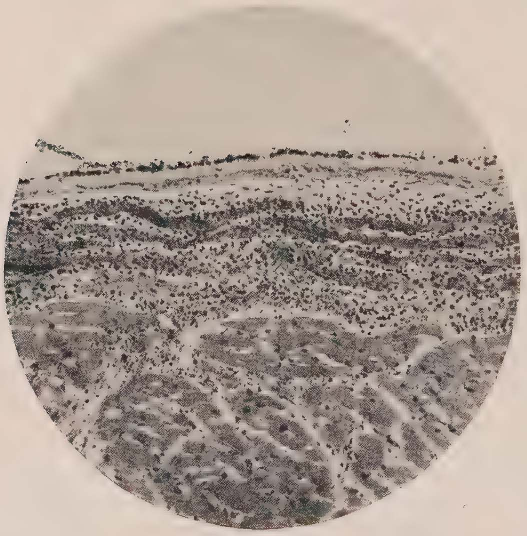

FIG. 217.—Inflammatory change round sub-endocardial branch of auriculo-ventricular bundle in a case of diphtheria. Note cellular infiltration round necrosed fibres. (A. C. L.) × 110.

small and contain only a few nuclei or a convoluted nucleus. The leucocytes are mainly lymphocytes and mononuclears, though a few polymorpho-nuclears also occur. At a later stage the nodule becomes more and more fibrous. Such is the Aschoff body in its typical form, but there also occur more diffuse lymphocytic infiltrations along the connective tissue planes, and the formation of nodules is often associated with an inflammatory œdema which may implicate the endocardium and lead to important results (p. 346). It is of importance to note that in the nodules it is not possible to demonstrate bacteria. It is thus seen that the rheumatic lesions are characterised by focal proliferations on the one hand, and by more diffuse inflammations and œdema on the other. Fibrosis is the natural sequel.

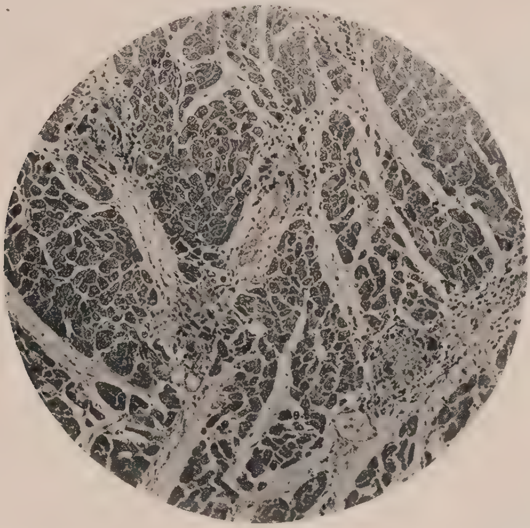

FIG. 218.—Rheumatic myocarditis showing several Aschoff bodies and interstitial fibrosis. (A. C. L.) × 80.

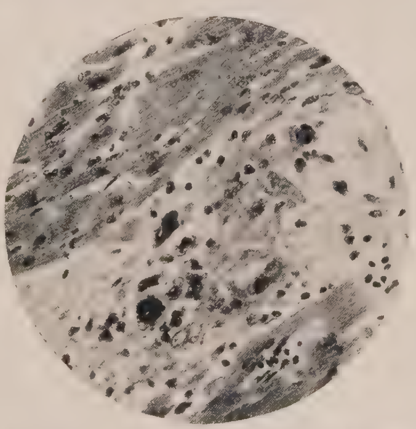

FIG. 219.—Aschoff Body in Child's Heart, showing characteristic Cells. (J. W. S. B.)

Rheumatic lesions in the myocardium are often accompanied by, in fact lead to, endocarditis and pericarditis (*vide infra*). (The accounts of acute vegetative and chronic endocarditis, and of pericarditis, may be read with advantage along with the account of the myocardial lesions.)

Sometimes in cases with a history of previous acute rheumatism, patches of white fibrous tissue with ill-defined margin are present all over the lining of the heart, and these are probably produced in a similar way. These sub-endocardial fibrous lesions may bring about effects by interfering with the ultimate arborisations of the conducting system. In various streptococcal infections, one may find small inflammatory foci with many polymorpho-nuclears present, and it is likely that in many instances these do not go on to suppuration but undergo a process of healing, the streptococci being killed off. Here also fibrosis may result. Whilst important structural changes are produced in the heart muscle by acute infections, it must be recognised that toxic action in these conditions may produce molecular alterations which are not demonstrable by microscopic methods. Thus morbid histology cannot explain all the clinical phenomena.

Chronic myocarditis is more conveniently discussed after lesions of the coronary arteries (p. 343).

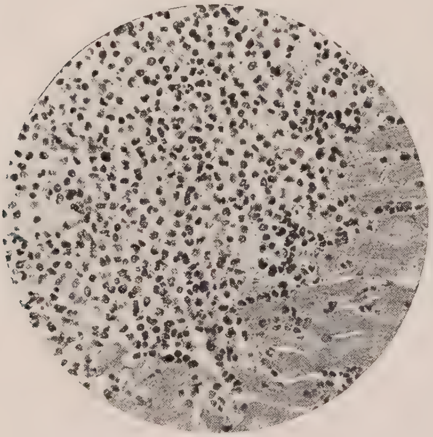

Fig. 220.—Acute Suppurative Myocarditis.

To left of field is a collection of pus; to right necrotic fibres are in process of liquefaction and disappearance. × 250.

Acute Suppurative Myocarditis. This may be due (*a*) to direct extension of pyogenic organisms from an adjacent valve, or (*b*) to infection by way of the blood stream. In the former case, the vegetations in bacterial endocarditis come to infect the adjacent endocardium, which often shows hæmorrhagic areas with crumbling vegetations; the organisms may then invade the muscle substance, giving rise to ulceration or abscess. In this way rupture of the heart may occasionally be brought about, especially in staphylococcus infection; perforation of the interventricular septum also has been met with. As has been mentioned above, a similar infection of the beginning of the aorta may occur, and acute aneurysm may result (p. 312). In cases of pyæmia, infective emboli may lodge in any of the branches of the coronary arteries, and abscesses of varying size may thus result; usually they are small (Fig. 220). In acute pyogenic infections, especially in those due to staphylococci, e.g. in acute suppurative osteomyelitis, etc., the myocardium is often affected as the result of cocci settling in the walls of the capillaries, rather than by embolism in the ordinary sense. And it is interesting to note that similar lesions occur when a suspension of staphylococci is injected into the vein of a rabbit, the heart muscle being probably affected next in order of frequency to the kidneys. Such small abscesses are met with especially in the posterior wall of the left ventricle near the base, and their presence is often indicated by the occurrence of small hæmorrhages into the epicardium, which, on being incised, show underlying areas of necrosis and suppuration. This is a point of some importance as, when merely the ordinary incisions are made in the examination of the heart, their presence may be overlooked ; epicardial hæmorrhages should always be carefully examined and cut into. The papillary muscles also are a not uncommon site of suppurative foci. Small abscesses may become absorbed and small cicatrices be left, but, of course, such abscesses occur especially in the infections which go on to a fatal termination. Abscesses of larger size, usually attended by hæmorrhage, are sometimes produced by grosser septic infarction (Fig. 221).

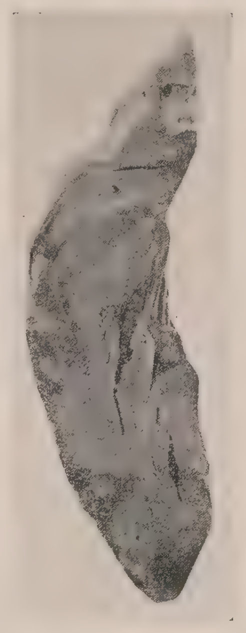

Fig. 221.—Longitudinal section of Wall of left Ventricle, showing pale septic Infarctions with Hæmorrhage around. × $\frac{2}{3}$.

Lesions of the Coronary Arteries

These are of special importance on account of the very serious results which may be produced in the cardiac muscle. They are the most fruitful cause of fibrosis of the myocardium, and thus it is convenient to describe them before fibrosis in general is considered.

(*a*) The lesion may be at the *origin of a coronary artery*, and then the greater part of the territory supplied by it will be affected ; or (*b*) there may be multiple or diffuse lesions of the *branches.* Furthermore, a blocking may be suddenly produced or there may be a gradual narrowing ; and the effects will vary accordingly. *Sudden blocking* of the orifice of a coronary artery may be brought about by embolism, or perhaps more frequently by a portion of attached thrombus or vegetation at the beginning of the aorta falling over the opening. The result will be sudden death. A *gradual stenosis* at the commencement of the coronaries is often produced by chronic disease of the adjacent part of the aorta, the orifice being implicated in a syphilitic or atheromatous patch or cicatricial area, and thus becoming slowly nipped. This is one of the two chief ways in which syphilis leads to serious cardiac disease, the other being by spread of syphilitic disease of the aorta to the aortic cusps. Normally, there is a certain amount of anastomosis between the two coronary arteries by means of their branches, but when the orifice of one coronary artery undergoes gradual narrowing, this becomes increased. Thus cases occur where the right coronary may be completely occluded; and on injecting the left coronary, it will be found that the fluid passes readily into the area supplied by the right. Gradual occlusion of the left coronary produces more serious results, and cannot occur to the same extent without bringing about a fatal result.

When narrowing of the left coronary is gradual, the usual result is atrophy of the muscle cells and secondary fibrosis; these changes, however, owing to a certain amount of anastomosis, are not co-extensive with the distribution of the artery, the effects being most marked in the anterior wall of the left ventricle near the apex. The wall becomes slowly thinned, somewhat stretched and stiffened, whilst the columnæ carneæ are attenuated and fibrous. In extreme cases the muscle may practically disappear in some parts of the wall, and much thinning may result. Such a condition may go on to rupture, and, in all cases where fibrosis is present, the formation of cardiac thrombi in relation to the affected areas is of common occurrence. The effect described forms one of the best examples of the relation of fibrosis to deficiency of blood supply, and although it is often spoken of as a *replacement* fibrosis, it must be regarded as, to a large extent, of compensatory nature, the fibrous overgrowth representing an attempt to make up for the loss of support produced by the atrophy of muscle. In view of its mode of production, it is also spoken of as *dystrophic* fibrosis.

Lesions of the branches of the coronaries due to atheroma, arterio-sclerosis or calcification, are very common, and here also the resulting destruction may be either complete or partial. The *total occlusion* of a coronary branch may be due to local thrombosis or to embolism, the former being much the more frequent. If the branch be sufficiently large, the cardiac action may be much interfered with, and sudden death may follow. If this does not happen, the common effect is the formation of an infarction in the heart wall. Such infarctions are of somewhat irregular form and affect mainly the inner two-thirds of the wall. The necrosed tissue becomes of a dull yellowish colour, while congestion and a certain amount of hæmorrhage are commonly present at their margin. Even when the infarction extends to the inner surface of the heart, there is to be found a thin layer of one or two rows of muscle cells which have escaped necrosis, as they are nourished directly through the endothelium from the blood contained within the heart. Later, connective tissue proliferation takes place around the dead tissue, and the latter gradually undergoes absorption; and it is to be noted that fibrous tissue often extends irregularly into the adjacent parts, probably as the result of the additional strain caused by the local weakening. If the in-

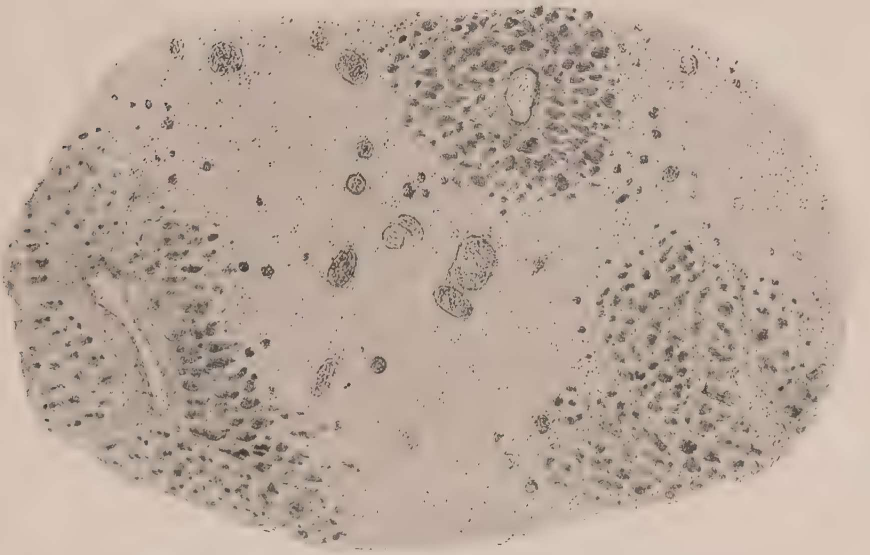

FIG. 222.—Fibrosis secondary to Arterial Disease, showing groups of surviving Muscle Fibres round the Blood Vessels. (C. and R.) × 50.

farction is of comparatively small size, the necrosed centre may in time completely disappear and a fibrous patch remain. Infarctions are commonest in the wall of the left ventricle, especially towards the lower part, and the septum is often involved. Sometimes the infarction undergoes autolytic softening, a condition known as *myomalacia cordis.* The endocardium over such a softened area may give way, the blood may pass into the softened area, and ultimately rupture of the heart wall may occur.

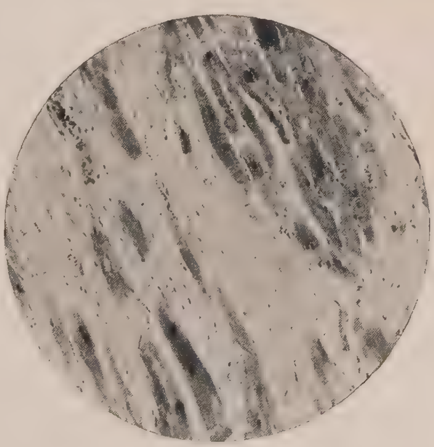

FIG. 223.—Fibrosis of Myocardium secondary to Disease of Coronary Arteries.

The muscle fibres are largely replaced by fibrous tissue and some of them are undergoing hypertrophy. × 250.

When the twigs of the coronary arteries are *slowly* narrowed, as often happens in the diseases mentioned, the effects correspond to those already described in the case of stenosis of the orifices. There results a starvation atrophy of the muscle fibres with secondary fibrosis, and in this way there may be produced numerous fibrous patches. The fibrosis in such cases is usually most marked in the parts farthest from the small arteries, i.e. it is pararterial in distribution (Fig. 222), and sometimes an artery may be seen to be surrounded by surviving muscle. The muscle cells which remain often show distinct hypertrophy of compensatory nature (Fig. 223). On the whole, the part which suffers most is the apex of the left ventricle, and here the wall may be fibroid over a considerable area. In the great majority of cases of patchy fibrosis visible to the naked eye, the cause is disease of the coronary branches, and, as explained, the fibrosis may be secondary to actual infarctions, or simply to starvation atrophy (Fig. 224).

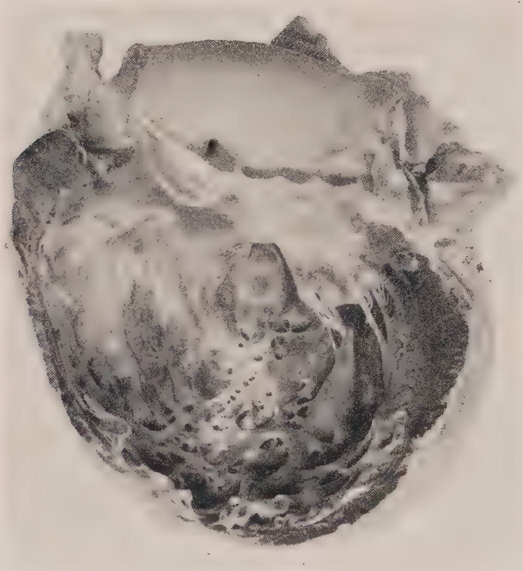

FIG. 224.—Extensive Fibrosis of Wall of left Ventricle with marked Thinning at places; secondary to Disease of left Coronary Artery. × $\frac{2}{3}$.

When the wall of the left ventricle becomes at any place extensively fibrosed, it is apt to undergo stretching and thinning (Figs. 225, 226). The result is that a local bulging is formed, the wall of which is thin as compared with the rest of the ventricle; in other words, an 'aneurysm of the heart' is produced. This may rupture and lead to fatal hæmorrhage into the pericardium. Another common result of fibrosis is the formation of thrombi over the affected areas. These, which are often multiple, occur especially in the depressions between columnæ carneæ. They may be rounded and fairly firm—cardiac polypi—or they may be more irregular and friable (p. 32). Patchy fibrosis of the myocardium is often associated with hypertrophy of the left ventricle, both conditions being the result of arterio-sclerosis.

The *functional effects* of coronary artery disease are varied, but the three chief may be said to be (*a*) sudden death, (*b*) angina and other symptoms of cardiac distress, and (*c*) gradual heart failure.

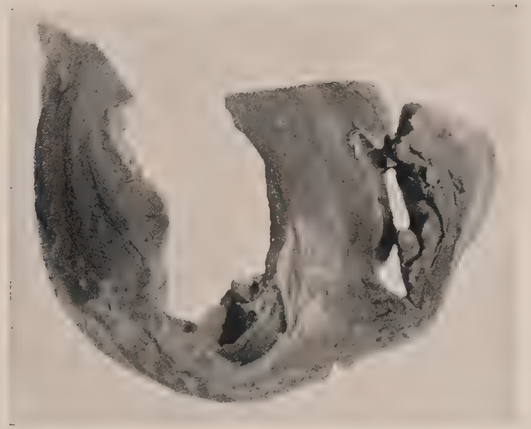

Fig. 225.—Transverse section of Left Ventricle, showing Fibrosis and Thinning of Myocardium; aneurysmal pouch containing thrombus is in process of formation.

(*a*) *Sudden death* may be due to some added condition such as thrombosis in a branch, or actual plugging of an orifice, or rupture of the heart; but in many cases it is simply the result of some extra exer-

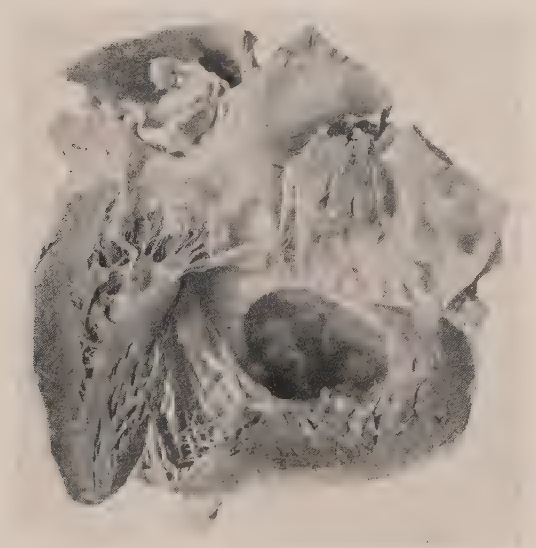

Fig. 226.—Aneurysm of Wall of left Ventricle, secondary to Fibrosis of Myocardium—the result of Coronary Artery Disease. × $\frac{2}{3}$.

tion acting on a heart with little or no reserve power and with blood supply just sufficient to maintain its activity. Thus sudden death from this cause is not uncommon when an orifice of a coronary artery is much narrowed, or when the lumen of a large branch is much encroached on by atheroma. The latter is commonest in the anterior descending branch of the left coronary just beyond its origin. It seems possible that by the impinging of the heart on the chest wall at this point, an artery already diseased suffers what may be called slight traumatism and thus the lesion is increased ; it is certainly the case that atheroma in this situation is often more marked than elsewhere.

(*b*) The deficiency of blood supply to the fibrosed heart muscle may lead to an attack of *angina,* often precipitated by exertion, and probably to be ascribed to functional ischæmia. Death may occur in such an attack. In addition, a more prolonged attack of pain and cardiac distress may result from *thrombosis of an arterial branch with infarction.* Such an attack may lead to death after a varying period of time or may be followed by relative recovery. The pain, which is severe and continuous and may last a considerable time, has been ascribed by Lewis to relative ischæmia of the cardiac muscle. He has shown in the case of voluntary muscle that severe continuous pain may be produced by repeated muscular contraction when the circulation is arrested, and that this is due to something, probably of the nature of metabolites, which accumulates in the tissue spaces. Restoration of the circulation leads to disappearance of the pain. A similar principle would appear to explain the pain from sudden coronary obstruction and also the pain which may arise when, with impaired blood supply, the heart's action is increased, there being in this case relative ischæmia ; the cardiac contractions being constant, the pain will persist so long as the part is ischæmic. The interior of an infarct becomes insensitive as it dies, but the living tissues at the margin are in a state of relative ischæmia. He has applied the same principle to the angina of sudden and passing type which is met with in cases of aortic disease and other conditions. Coronary thrombosis may be attended by a certain degree of pyrexia and leucocytosis, probably the results of the absorption of products of autolysis from the necrosed muscle.

(*c*) In myocardial fibrosis, however produced, a common result in course of time is *dilatation of the ventricles* with secondary incompetence of the mitral and tricuspid valves, and death often results from gradual heart failure attended by œdema, etc., that is, from decompensation (p. 357).

The actual size of the heart in disease of the coronary arteries varies and depends chiefly on associated conditions. If general arterio-sclerosis with hypertension has been present, hypertrophy, or hypertrophy with dilatation, will most likely be a marked feature. On the other hand, when the lesion has been degenerative atheroma the heart may be little increased in size.

Chronic Specific Infections

Syphilis. In syphilis, gumma may occur in the heart, although it is comparatively rare. The commonest site is in the septa, especially the inter-auricular septum, where it may reach a considerable size, so as to form a tumour-like mass which may bulge into both auricles. In this position it may come to affect the conducting system and cause heart-block. It may be met with also in the wall of a ventricle. In syphilis there is sometimes a fairly diffuse or a patchy fibrosis; this is to be regarded as a chronic interstitial inflammation, such as is caused by syphilis elsewhere, although it may be in part the result of arterial changes. The syphilitic nature of a fibrosis, apart from gumma, cannot, however, be determined with certainty, unless the spirochætes are found; it can only be inferred from associated lesions. In *congenital syphilis* the spirochætes are often numerous throughout the cardiac muscle, occurring in clumps here and there. There may be little change around them, but in some cases a considerable amount of proliferation of the connective tissue may be present, analogous to what occurs in the liver and lungs. Gummata also may be met with; they may be of the miliary type (Fig. 228) or may reach a considerable size. Manifestly such lesions may be the cause of fibrosis at a later period, in cases where the patients survive. There is also evidence that syphilitic infection during intra-uterine life is responsible in a proportion of cases for congenital abnormalities of the heart; apparently

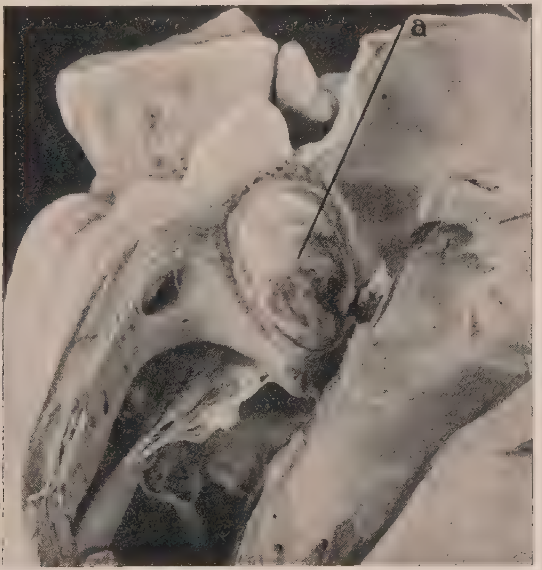

FIG. 227.—Syphilitic Gumma (*a*) of Heart in Right Ventricle at its Base.

in some way the presence of spirochætes may disturb the normal process of development.

Opinion varies greatly with regard to the frequency and importance of syphilitic lesions of the myocardium; possibly their incidence varies in different localities. Warthin, who has studied the subject widely, found them to be common and demonstrated spirochætes in a large proportion of cases. Other observers have, however, obtained opposite results. Our own experience is that the proportion of myocardial lesions, actually syphilitic in nature, is relatively small. Certainly, in the great majority of cases of 'heart disease' caused by syphilis, the condition is due to the aortic valve being affected secondarily to disease of the aorta; in a certain proportion to implication of the orifices of the coronary arteries.

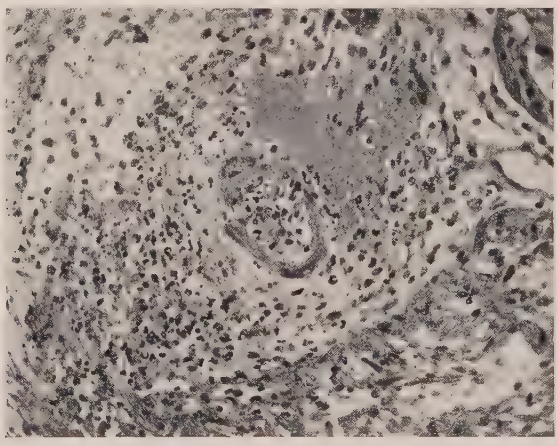

Fig. 228.—Miliary Gumma of Heart of Child.

In centre of field there is a small thrombosed arteriole and above it necrotic change is spreading. (J. W. S. B.) × 200.

Tuberculosis. The heart muscle enjoys a relative immunity against tuberculous infection. Even in miliary tuberculosis, when the nodules are very numerous in the various organs, they are few or absent in the heart wall; their occurrence on the heart valves and in the endocardium has been described, but is very rare. Secondary infection by tubercle bacilli of vegetations on the valves has occasionally been met with. Solitary or conglomerate tubercle in the myocardium also has been described, but such an occurrence is quite exceptional. Occasionally there is a diffuse lesion with little caseation, accompanied by obliterative changes in the small arteries. In the absence of discoverable tubercle bacilli in such lesions it may be difficult to distinguish it from a gumma. Tuberculosis of the pericardial sac due to retrograde extension from lymphatic glands is, however, not infrequent, as will be described below (p. 374).

Fibrosis of Myocardium

(‘ Chronic Interstitial Myocarditis.’)

We may now summarise the chief causes of overgrowth of connective tissue in the heart wall. The term ‘ fibrosis ’ is preferable, seeing that in many cases the condition is merely secondary to atrophy of the muscle. When the fibrous patches are of considerable size, by far the commonest cause is some lesion of the coronary arteries, which has resulted either in an infarction or starvation atrophy. The characters of this form of fibrosis have just been given. Fibrosis may also be the result of the acute infective lesions described above, especially those of acute rheumatism. In such cases the areas of fibrous tissue are of comparatively small size, and the condition may be often discoverable only on microscopic examination. Sometimes, however, there may be recognisable naked-eye changes. In the small fibrous areas, which are usually around the small arteries, the muscle fibres are found to have disappeared, and there may be considerable new formation of capillaries ; leucocytes, chiefly lymphocytes and plasma cells, may be fairly numerous. The fibrosed patches may occur throughout the cardiac muscle, but are usually most abundant in the inner part ; especially is this the case in the post-rheumatic affections, in which they are not uncommon underneath the endocardium. Local fibrosis also may be secondary to pericarditis or to endocarditis. In the case of the former, the superficial layer of muscle may be invaded by young connective tissue which becomes fibrous. The extent to which this takes place, apparently depends on the degree to which the muscle has been damaged by the pericarditis, but it is rare for any considerable degree of fibrosis to be produced in this way.

Extension from the valves in cases of chronic endocarditis is of common occurrence, the parts most affected being the apices of the papillary muscles and, what is of more importance, the parts of the ventricular walls adjacent to the attachment of the affected valves. Thus, the fibrosis may spread deeply into the septum and involve the conducting system (p. 364). Fibrosis may be produced also by syphilis (*vide supra*). In addition, however, there occur cases of considerable fibrosis in which the cause cannot be determined.

These various fibrous changes, in addition to producing local effects, e.g. aneurysm, rupture, thrombosis, etc., interfere with the cardiac efficiency according to their degree. And though there may be considerable hypertrophy of the intervening muscle, dilatation of the heart with secondary incompetence of the mitral and tricuspid valves is a common result. The fibrous lesions may act also by implicating the conducting system of fibres, either the auriculo-ventricular bundle itself or the branches of the same.

II. LESIONS OF THE VALVES

Endocarditis. Acute endocarditis is essentially an affection of the valve structures, though the endocardium of other parts may be similarly affected. It is characterised by the formation of thrombi of varying structure on the injured endocardium ; these are known as *vegetations.* Two main types of the condition are to be recognised. (*a*) One type is due to rheumatism and has definite features, being characterised by the presence of small firm vegetations. The mode of formation of these will be afterwards discussed, but at present we may say there is not sufficient evidence that bacteria are concerned in their production. The condition is also spoken of as *simple* or *vegetative endocarditis.* We cannot say definitely that cases of endocarditis of this type are all due to rheumatic infection, but there is increasing evidence that this is the case. (*b*) The other type is characterised by the presence of vegetations which are larger and more extensive in their distribution and of more crumbling character. An essential feature is the presence of bacteria in large numbers on the surface and in the substance of the vegetations. The bacteria which are the cause of the lesions are of various kinds, but belong chiefly to the pyogenic group and can be readily cultivated. The term *bacterial endocarditis* is generally now applied to this form ; 'malignant' or 'ulcerative' were terms formerly in common use. Bacterial endocarditis varies greatly in its intensity and in the severity of its effects, and this depends mainly on the nature of the bacteria present. Two varieties are, however, conveniently distinguished, namely, a *subacute* and an *acute.* This distinction is a suitable one in view both of the etiology and also of the associated lesions and the general course of the disease.

There is further a *chronic endocarditis* characterised by fibrosis of the valve segments and other parts. (*a*) This is frequently the result of acute endocarditis, and then in the great majority of cases acute rheumatic endocarditis is the antecedent condition. There is a possibility, that occasionally subacute bacterial endocarditis may pass into a healing stage with fibrosis ; this, however, if it occurs, is rare. (*b*) Again, a chronic endocarditis may not be preceded by an acute attack, but may be of a slowly progressing nature throughout. These two varieties of chronic endocarditis can thus be spoken of respectively as *secondary* and *primary* chronic endocarditis or valvulitis.

We shall now consider the structural changes in these varieties of endocarditis and discuss their etiology.

Acute Endocarditis. (*a*) VEGETATIVE (RHEUMATIC) TYPE. As has already been said, this is chiefly of rheumatic origin, although in a certain proportion of cases a rheumatic history may not be obtained. It is characterised by the formation of small vegetations on the valves, which occur first as minute rounded bodies of greyish or pinkish-grey translucent appearance, and which are formed first along the lines of contact of the segments (Fig. 229). Thus in the case of the aortic valve, they are found on the ventricular aspect of the cusps a short distance from the free margins, and in the case of the mitral on the auricular aspect. The vegetations afterwards increase in size and may extend on the endocardium ; for example, from the mitral valve they may spread over the auricular aspect of the curtains to the lining of the auricle, especially on the posterior aspect. In cases examined at an early stage the valve segments have been found to be swollen owing to the presence of inflammatory œdema. This is succeeded by general thickening of the connective tissue. The vegetations are, in the first instance, essentially slowly formed thrombi, and are composed chiefly of altered blood platelets (p. 37), though there may be an addition of exudate from the inflamed valve. At a later stage organisation takes place from the valve. In rheumatic endocarditis there is a marked tendency to recurrence of attacks.

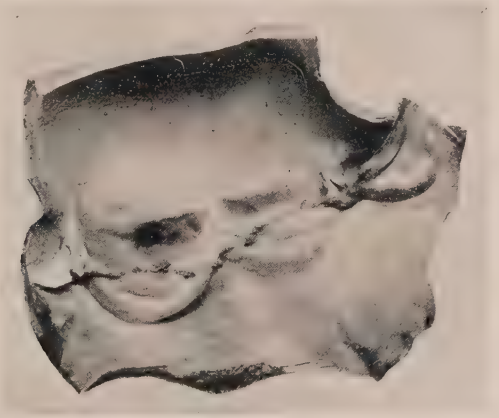

Fig. 229.—Acute Rheumatic Endocarditis of Aortic Valve, showing small vegetations along lines of contact.

Rheumatic endocarditis is essentially an affection of early life, the second decade, according to Thayer, being that of maximum incidence ; the serious results of the lesions, however, may not appear till a much later time of life. In the great majority of cases there is a definite history of rheumatism or of chorea, which is a rheumatic manifestation, but sometimes no such history is obtainable. The valves of the left side of the heart are much more frequently affected than those of the right, the mitral more commonly than the aortic. The tricuspid is much less commonly involved, while affection of the pulmonary is very rare. The definite relationship of the vegetations to the lines of contact of the valve segments is clear evidence that the pressure along these lines on closure of the valves is a determining factor in the deposition of the vegetations. It acts as a slight trauma on the surface endothelium altered by subjacent inflammatory œdema, and then the lesion thus resulting leads to the deposition of platelets. This factor will naturally be of greater effect on the left side of the heart where the blood pressure is higher; and the more frequent implication of the mitral has been ascribed to its greater vascularity. The inflammatory œdema, which is part of a similar affection of the adjacent myocardium, is soon followed by proliferation of fibrocytes and, it may be, by the formation of Aschoff bodies especially near the base of the valve segments.

In a very acute case of short duration which I have recently seen inflammatory œdema tended to be most marked in the subendothelial layer, there being here localised swellings almost like vesicles or blebs especially near the vegetations. The appearance was as if the surface of the swollen patches had given way owing to the slight trauma from the closure of the valve (Fig. 230). Such an affection of the valves accounts readily not only for the site of the vegetations but also for the general fibrotic thickening of the valves which follows and which is so characteristic a feature in rheumatic cases (p. 350).

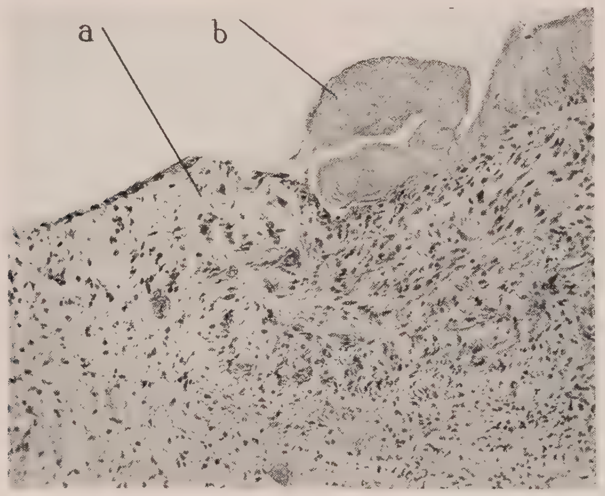

FIG. 230.—Section of Mitral Valve in Early Acute Rheumatic Endocarditis, showing (*b*) a small vegetation with commencing organisation. To the left side there is a patch of œdematous swelling (*a*) such as apparently precedes the deposition of platelets. (A. C. L.) × 60.

(*b*) BACTERIAL TYPE. Here the vegetations are larger and more extensive and tend to break down; thus the valve segments may be largely covered by crumbling masses (Fig. 231). The substance of the segments may become softened and eaten away; or, especially in the case of the aortic, rupture may take place, leading to severe incompetence. Aneurysm of a valve is another common result, the organisms causing a softening of one side of the curtain, so that the thin tissue is stretched by the blood pressure and forms an aneurysmal bulging. An aneurysm or rupture of a valve is sometimes obscured by vegetations. In the case of the aortic segments the aneurysm will bulge downwards into the ventricle, owing to its being subjected to pressure during diastole. An aneurysm of the mitral valve will bulge towards the auricle, as the stretching occurs during the ventricular systole. Subsequent rupture may give rise to perforation. The vegetations may spread also to the chordæ tendineæ, and softening and rupture of them may take place. Infection of the intima at the commencement of the aorta may occur by extension, or by direct contact from a vegetation, and an acute aneurysm may be formed (Fig. 232). The organisms may also pass directly into the substance of the heart wall, and lead to ulceration or to abscess formation. This is especially met with in infections with staphylococci and the hæmolytic streptococci. The destructive changes described are most marked in the acute type of the disease, whilst in the subacute type extensive formation of vegetations is usually a prominent feature. In both types

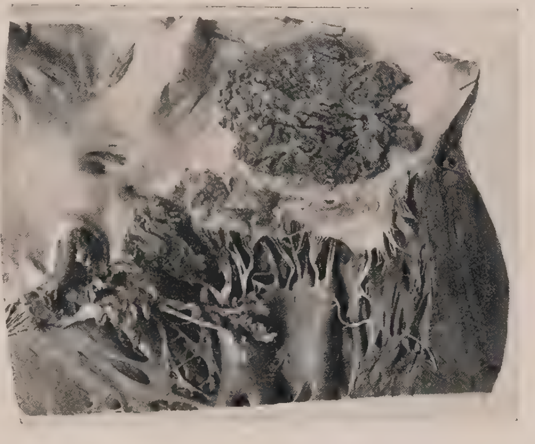

Fig. 231.—Bacterial Endocarditis of Mitral Orifice.

The valve seen from auricular aspect shows crumbling and ulcerating vegetations ; a large mass is present on wall of auricle.

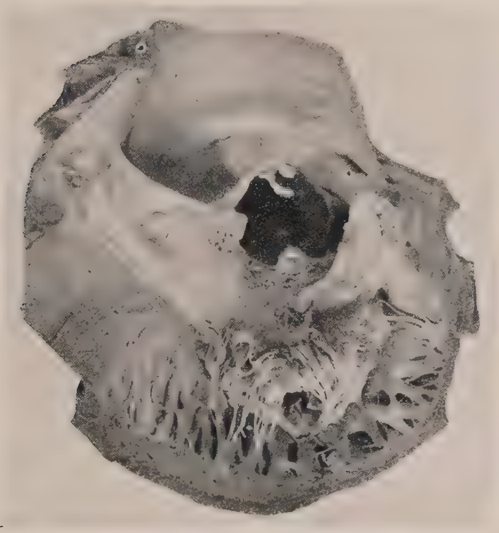

Fig. 232.—Chronic and Bacterial Endocarditis of Aortic Valve, with ulceration and formation of Acute Aneurysm at beginning of Aorta.

of bacterial endocarditis the valves most often affected are those on the left side of the heart. Affection of the tricuspid, however, is not uncommon, but vegetations on the pulmonary are of rare occurrence.

Acute bacterial endocarditis is ordinarily produced by the pyogenic organisms, those most frequently concerned being *hæmolytic streptococci*, the *Pneumococcus* and *Staphylococcus aureus*. It is occasionally due also to other organisms such as gonococcus, typhoid bacillus or coliform organisms. Infection of the valves is in most cases secondary to some other lesion caused by one of these organisms; it thus occurs in septic conditions, osteomyelitis, pneumonia, etc. Occasionally, however, the path of infection is obscure. Virulent organisms can attack previously healthy valves, as is shown by experimental work, but a pre-existing lesion may sometimes be found. Not infrequently the lesions are localised to one part of a valve or more irregularly disposed than in the other forms of endocarditis; for example, there may be massive vegetations at the junction of two aortic cusps, the rest of the valve being free. On the whole, the most severe and rapid examples are due to the *Staphylococcus aureus* and the *Streptococcus hæmolyticus*, the latter being the more frequent cause. The staphylococcus especially tends to produce destructive change and a softening of parts, ulceration into the myocardium, etc., whilst it causes secondary abscesses in various organs more frequently than any of the other bacteria. Endocarditis, due to *Staphylococcus albus*, is comparatively uncommon; it is of a much milder type and may run a protracted course. *Pneumococcal endocarditis*, which usually has acute pneumonia as its antecedent, is characterised by massive vegetations which are somewhat soft and may be of a greenish tint. Large portions may be detached as emboli and the resulting infarctions only occasionally show suppurative change. *Gonococcus* also leads to the formation of large vegetations, with destructive effects; endocarditis produced by this organism is, however, rare.

Embolism, of course, is of common occurrence, and the resulting infarctions often undergo suppuration; multiple small abscesses may also be present in organs.

Subacute bacterial endocarditis is, in the vast majority of cases, produced by non-hæmolytic streptococci, and of these the *Streptococcus viridans* is the type most commonly met with. Infection probably takes place from the mouth, naso-pharynx or possibly alimentary canal, where such organisms normally are present, but in most instances the path of infection is quite obscure. It is noteworthy, however, that in most instances some previous abnormal state of the valves can be detected which acts as a focus of diminished resistance and aids the infection. This may be the result of previous rheumatic infection, or it may be a congenital abnormality, as has been shown especially by Grant, who found that in a considerable proportion of cases there was congenital fusion of two aortic segments. The vegetations are larger, softer and more crumbling in character than in the rheumatic form. They tend to spread on the endocardial surface, but the destructive changes of the acute bacterial form are less in evidence. Embolism is of common occurrence and the infarctions do not undergo suppuration.

Subacute endocarditis, which appears to have become a much commoner affection in recent times, runs a course of a month or two and is attended by a fairly definite syndrome. Pyrexia of irregular type is present and there is usually a distinct leucocytosis which likewise varies. As a rule the spleen is enlarged and is sometimes markedly so (p. 493). Non-hæmolytic streptococci can usually be obtained in blood culture, but sometimes the result is negative and cultures have to be repeated. In addition to embolism of a gross type there is also embolism of capillaries by the cocci. Petechiæ in the skin, which are fairly common in the disease, are due to this cause (Fig. 233). A form of nephritis of focal character is another important complication produced in a similar way. It is accompanied by hæmaturia of varying degree (p. 668). In subacute bacterial endocarditis we have examples of lesions from which the organisms are supplied to the blood stream, giving rise to a bacteriæmia. They are unable, however, to multiply in the blood and cause a rapidly fatal septicæmia; on the contrary, they are constantly being destroyed in the spleen and elsewhere, and it has been shown that the reactions of general immunity are stimulated and antibodies are present in the blood. But the organisms in the substance of the vegetations, in what is practically dead material, are not affected thereby; they continue to grow and be discharged into the blood stream. In a few cases of subacute bacterial endocarditis, bacilli of the influenza type have been found to be the organisms present.

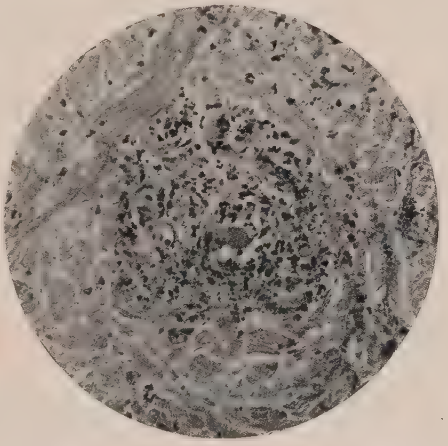

FIG. 233.—Section through hæmorrhagic spot in cutis in subacute bacterial endocarditis. Note small thrombosed and degenerate arteriole surrounded by leucocytes—the result of infective embolism. (A. C. L.)

In addition to the important types of endocarditis described, one may mention that the presence of a few vegetations on the mitral and aortic segments is not uncommon in cases where death has occurred from wasting diseases. The vegetations are usually patchy in character and somewhat soft. This occurrence is to be regarded as a terminal phenomenon due to reduced resistance and aided by degenerative changes in the curtains.

Chronic Endocarditis. This type of lesion is characterised by overgrowth of the connective tissue and its subsequent contraction. It is often the sequel to acute endocarditis, usually of the rheumatic type, which is specially prone to lead to a progressive induration. In a certain proportion of cases, however, the condition is of slowly progressive nature from the outset, this being especially the case with the aortic valve, as will be described. The chronic inflammatory process may lead to thickening and retraction of the valve segments, and thus interfere with efficient closure; *incompetence* thus results. On the other hand, the adhesion between the segments may cause narrowing or *stenosis* of the aperture. Both effects are not infrequently present together. It is to be noted that distinct stenosis is ordinarily the result of rheumatic infection, being brought about by the general inflammation of the substance of the valve. In fact, we are inclined to the view that typical mitral stenosis is always produced in this way.

At the *aortic* orifice *stenosis* is relatively less common than at the mitral, probably owing to the fact that the segments are forcibly thrown apart at the ventricular systole. In some cases, however, the segments become adherent at their adjacent margins, and ultimately the aperture becomes triangular or 'bayonet-shaped' and considerably reduced (Fig. 234). Along with this there is usually a degree of *incompetence* of the valve, although in certain cases the obstruction is the chief result. Aortic incompetence is a very common lesion and may be brought about in various ways. The margins of the segments may become more or less thickened and shortened, occasionally tacked down at their extremities, the result being that the segments can no longer come into apposition. Incompetence may be brought about also by rupture of a valve segment or by perforation. Further, occasionally the thickened valve segments become stretched, so that their margins are, as it were, too long and are somewhat pendulous. In this way very marked incompetence may result.

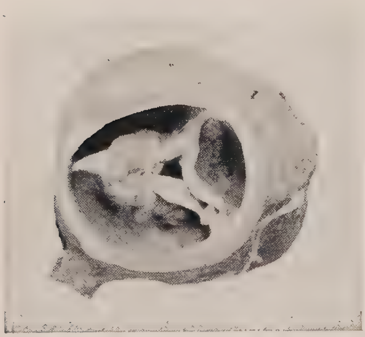

FIG. 234.—Chronic Endocarditis of Aortic Orifice with great stenosis and secondary calcification.

In the case of the *mitral* valve, adhesion of the segments is of very common occurrence, and the resulting stenosis may reach a great degree. The orifice may sometimes measure as little as 0·4 inch or even less in diameter, and as the actual size or area is in proportion to the square of the diameter, the reduction is extreme. Sometimes the segments are simply adherent, so that a cone or funnel-shaped structure is the result. In other cases the segments are shortened and form a sort of fibrous diaphragm with a slit-like aperture—‘button-hole’ mitral (Fig. 235). Along with the change in the curtains, there are usually marked thickening and shortening of the chordæ tendineæ, and also fibrous induration of the apices of the papillary muscles. In this way considerable rigidity of the valve is brought about. Some degree of incompetence is nearly always present with stenosis of the mitral, but often obstruction is the outstanding lesion. The fibrous thickening often becomes excessive, and lime salts may be deposited; occasionally the margins of the aperture are quite rigid. Recurrent attacks of endocarditis are common and at post-mortem examinations recent vegetations are often found on fibrosed valves and the auricular wall. The formation of thrombi in the failing auricles, especially the right, often follows and a rare occurrence of interest is the formation in the left auricle of a so-called ball thrombus which lies free in the cavity and which may reach an inch or more in diameter. Tricuspid stenosis also occurs in long-standing rheumatic cases. It is less common than mitral stenosis and the narrowing is less marked.

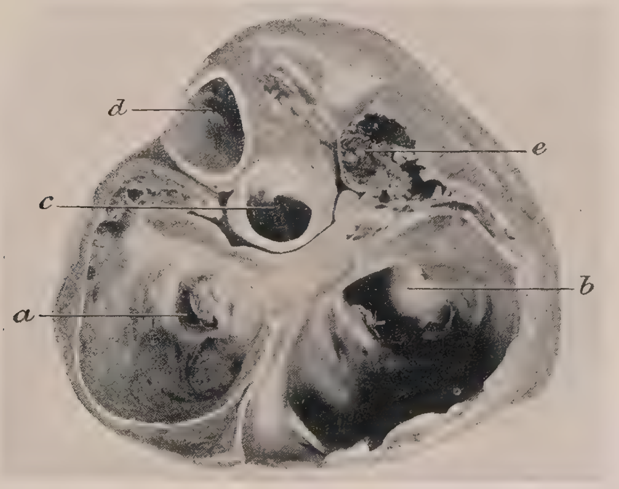

Fig. 235.—Horizontal section through Auricles in a case of Mitral and Tricuspid Stenosis, as seen from above.

a, mitral valve, much stenosed; *b*, tricuspid valve, somewhat stenosed; *c*, aorta; *d*, pulmonary artery; *e*, right auricular appendix containing thrombus.

Chronic endocarditis, in addition to occurring as a sequel to acute inflammation, may develop without any acute onset. Disease often extends from the aorta and implicates the valve; this occurs especially in syphilitic disease (Fig. 236), though also occasionally in atheroma. In *syphilis* this is a relatively frequent event, and thus it is that a positive Wassermann reaction is obtained in a comparatively large proportion of cases of aortic disease. Incompetence, sometimes of severe degree, is the common result, and this may be intensified by stretching of the aortic orifice as a result of the lesions in the wall of the aorta. We may say that implication of the aortic valve is one of the two most serious effects of disease at the beginning of the aorta, the other being narrowing of the orifices of the coronary arteries. It is doubtful whether syphilis affects directly the mitral valve; in fact, we believe that chronic endocarditis of this valve leading to any serious effect rarely occurs except as the result of rheumatic infection. Patches of thickening and degeneration are, however, comparatively common, and these may be attended by a certain amount of fibrosis, especially at the base of the curtains; calcification may follow. These yellowish patches of degenerative thickening affect especially the anterior segment and have a structure closely similar to that of an atheromatous patch of the aorta.

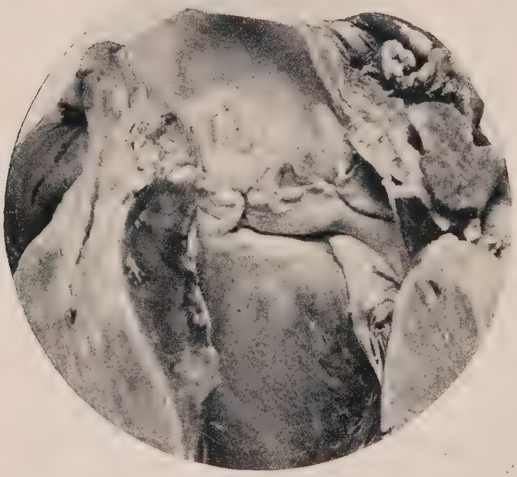

Fig. 236.—Chronic Syphilitic Disease of Aortic Valve and characteristic Syphilitic Lesion in the Aorta above.

Effects of Valvular Lesions. The various valvular lesions described, resulting in obstruction or incompetence, or in both combined, will manifestly interfere with the efficient pumping action of the heart, and accordingly processes of adaptation will come into play. The heart has remarkable powers of adjustment to the abnormal conditions, and by means of them the circulation may be satisfactorily maintained, that is, *compensation* may be established. The processes concerned are two in number, namely, increase in the thickness of the muscular wall or *hypertrophy* proper, and increase in the size of the cavity or *dilatation*. This compensatory dilatation is, however, to be clearly distinguished from that resulting from cardiac failure, and it would be better simply to call it *enlargement* of the chamber. In speaking of compensation one must, however, be careful not to assume that a condition equal to the normal is established. The circulation may be well maintained, and the heart may even be able to respond to additional calls made on it; but it is working at a disadvantage as compared with the normal state, its reserve power is probably always diminished, and it is apt to fail in the course of time or as the result of strain. Further, there are certain defects which cannot be compensated for, e.g. the pulmonary congestion in a case of mitral stenosis, as will be later explained. Before describing the effects on the heart of the individual valvular lesions, we shall consider the principles regulating the occurrence of compensatory hypertrophy and dilatation respectively.

(A) *Hypertrophy.* In the first place, an obstructive lesion may be compensated for by increased power of the chamber behind it, that is, by muscular hypertrophy ; in this way a normal amount of blood *may* be driven through a narrower aperture. Aortic stenosis is rarely seen without some incompetence, but sometimes it is the chief lesion, and then the main effect is hypertrophy of the left ventricle. The best example, of a pure obstructive lesion is seen in arterio-sclerosis and chronic kidney disease with high blood pressure ; increased resistance to the outflow from the left ventricle is present, and accordingly we often meet with a pure hypertrophy of the left ventricle without any enlargement of the cavity. In these conditions there may be no effect farther back in the circulation —no pulmonary congestion and no effect on the right side of the heart, so long as the mitral valve is competent. If, however, the actual output of blood into the aorta is diminished, as is the rule in aortic stenosis, there will be a certain excess of blood in the venous system, and if mitral incompetence becomes established, as is apt to follow, the effects of this will be added (p. 357).

(B) *Compensatory Dilatation.* In the second place, when there is regurgitation, say at the aortic orifice, it is evident that increased muscular power alone will not remedy the defect, and that a larger cavity will be necessary. For example, if a third of the blood regurgitates during diastole, two-thirds being actually passed on, a cavity of a size larger than the normal, in the proportion of 3 : 2, will be required in order that the normal amount of blood should be passed on ; that is, with the proviso that the ventricle is emptied at each systole and the normal rate of contraction is maintained. Theoretically, however, with a cavity increased in the proportion mentioned, a normal amount of blood might be circulated. Thus in aortic regurgitation there is enlargement of the left ventricle from the outset, and this is to be regarded as of compensatory nature and not, at least in the first instance, as the result of muscular failure. The enlarged ventricle requires a proportionate increase of muscular power and thus hypertrophy also occurs. The same principle holds with regard to mitral incompetence, and when this lesion is present along with aortic incompetence, the heart has to act under very unfavourable conditions.

(C) *Dilatation from Failure.* In the third place, the muscular power of any hypertrophied chamber may fail after a time. When increased work is thrown on the normal heart as in physical exertion, there is increased rapidity of the cardiac contractions, which are also more forcible, along with increased blood pressure in the arteries. Thus there is an increase in the cardiac output of blood—increased 'minute volume,' and this may amount to two or three times the normal. At first there is some increase in the size of the cavities, the muscle cells are stretched and there is response by greater discharge of energy (Starling). In the normal state the size of the cavities is soon regained, but if the heart is fatigued the cavities remain dilated. It can thus be readily understood how in a heart with valvular or myocardial disease dilatation may become progressive, and this may be accompanied by deficient emptying and deficient output of blood.

Cardiac dilatation due to muscle failure may occur also apart from pre-existing hypertrophy. Excessive strain or extreme physical exertion may bring about temporary dilatation with cardiac symptoms in a previously healthy heart, and this may be satisfactorily recovered from by rest in bed, though the effects sometimes last a considerable time. Further, a certain amount of dilatation occurs from the prolonged action of toxins as in fevers. Hearts with lesions of the myocardium, e.g. fatty or fibrous, are very prone to become dilated. In these instances cardiac dilatation, whether occurring secondarily to hypertrophy or as a primary condition, is to be regarded as the evidence of diminution of muscular efficiency. And it is to be noted also that on purely physical principles a dilated heart acts at a great disadvantage, as, in order to bring about a given pressure within the larger cavity, its wall has to be exposed to greater tension by contraction than that of a smaller. Another important effect which often follows dilatation of a ventricle, is stretching of the mitral or tricuspid orifice, as the case may be, and secondary or *relative incompetence* of the valve. With regard to the aortic and pulmonary valves, their competence can be readily tested in the post-mortem room by allowing water from the tap to flow into the corresponding vessel, the heart being kept in the upright position. Normally the stream of water will close the valve and the water will then be retained in the vessel. But in the case of the mitral and tricuspid valves there is no such mechanical method of testing, and we can judge roughly of their competence or incompetence only by the diameter of the orifice or by the actual structural changes present, such as thickening and contraction.

Measurement of the diameter of the orifices, which can be conveniently made by means of a graduated wooden cone, has only a relative value, but we have found that the mitral orifice rarely measures more than 1·3 in. (normal 1–1·2 in.) or the tricuspid more than 1·7 in. (normal about 1·5 in.) without there being evidence of incompetence during life. The following additional measurements will be of service in the examination of the heart. The diameter of the aortic orifice is usually 0·9 in., that of the pulmonary 1 in. The internal length of the left ventricle taken from the base of the aortic cusps to the apex is 3¼–3½ in., and the maximum thickness of its wall, about an inch below the auriculo-ventricular sulcus, is half an inch ; in the latter measurement the columnæ carneæ should be excluded and the thickness of solid muscle taken. The thickness of the right ventricle can hardly be satisfactorily measured, and when hypertrophy occurs it is shown more by increased thickness of the columnæ carneæ than of the wall. The normal weight of the heart of a woman is 9–10 oz., of a man 10–11 oz. ; the organ should be freed of blood and clots before it is weighed.

Effects of Individual Lesions. We shall now give some of the effects of the valvular lesions on the chambers of the heart. *Aortic stenosis* produces, in the first place, hypertrophy of the left ventricle, this being accompanied by thickening of columnæ carneæ and papillary muscles ; but as there is practically always along with it some incompetence, there is often a certain amount of enlargement of the cavity as well, which becomes somewhat lengthened and more pointed. Later, the hypertrophied muscle may fail and then dilatation is the prominent feature. The passage of the blood during systole through the narrow aortic orifice, gives rise to a murmur audible over the base of the heart, ventricular systolic in time (V.S.) and often of considerable intensity. *Aortic incompetence* produces, from the outset, enlargement of the cavity of the left ventricle, and this is accompanied by a varying amount of hypertrophy of the wall. The enlargement may be of great degree, the internal length reaching 4½ in. or even more. So long as the mitral valve is competent the effects of the aortic lesion may not extend backwards to the lungs and venous system ; but as the enlargement of the left ventricle progresses, and especially as the muscle fails, the muscular ring round the mitral orifice becomes stretched and secondary mitral incompetence results ; the effects of the latter lesion then become superadded. Or incompetence of the mitral from endocarditis may be present as a concomitant lesion, and in such a combination we meet with the most striking examples of enlarged heart—the so-called *cor bovinum*, the weight reaching 2 lb. or more. The pulse in aortic incompetence is characteristic. There is a large systolic wave owing to the increased output by the left ventricle, and this is followed by a rapid fall owing to the regurgitation. The pulse has to the finger a bounding and collapsing character —the so-called ‘ water-hammer pulse ’ or ‘ Corrigan's pulse ’—and there is a distinct dicrotic wave. A ventricular diastolic murmur (V.D.), corresponding with the regurgitation, is usually audible over the base of the heart, and there is often also a systolic (V.S.) murmur.

The effects of *mitral stenosis* are characteristic. The left ventricle gets less blood than normally and can easily pass it on. It accordingly does not undergo hypertrophy ; on the contrary, it is often rather atrophied. The left auricle is dilated (it readily becomes so) and slightly hypertrophied, whilst its endocardial lining becomes thickened and opaque. The work of driving the blood against the obstruction at the mitral falls on the right ventricle, which undergoes marked hypertrophy and later becomes dilated, while the tricuspid valve often becomes relatively incompetent, and marked pulsation may occur in the veins of the neck ; also the right auricle becomes much enlarged. The heart as a whole thus comes to have a somewhat quadrangular form. The enlarged right ventricle forms a larger proportion of the anterior surface of the heart than normally and often constitutes the apex, while the small left ventricle is applied, as it were, to the side of it (Fig. 237). The weight of the heart as a whole is relatively not so much increased as in other lesions. As the hypertrophied right ventricle has to propel the blood through the lungs against the obstruction in front, there is always in mitral stenosis passive hyperæmia of the lungs, and this cannot be obviated by any compensatory process. The lungs pass into the state of brown induration (p. 18), and there is often slight hæmoptysis, which, however, is to be distinguished from the more severe hæmoptysis met with as the result of infarction when the heart is failing. As the output from the left ventricle is diminished while the arterial pressure may be well maintained, there is an accumulation of blood in the venous system (p. 15)—general passive congestion, often associated with cyanosis, breathlessness on exertion, etc.; yet even with these conditions the patient may be little incapacitated, at least for a time. Later, when compensation begins to fail, the venous engorgement is increased and œdema of the cardiac type supervenes; and death is often preceded by thrombosis in the right ventricle or auricle and hæmorrhagic infarctions in the lungs. Sometimes thrombosis in the systemic veins occurs. In mitral stenosis the dilated right auricle not infrequently passes into a state of fibrillation (p. 364). Mitral stenosis usually gives rise to a

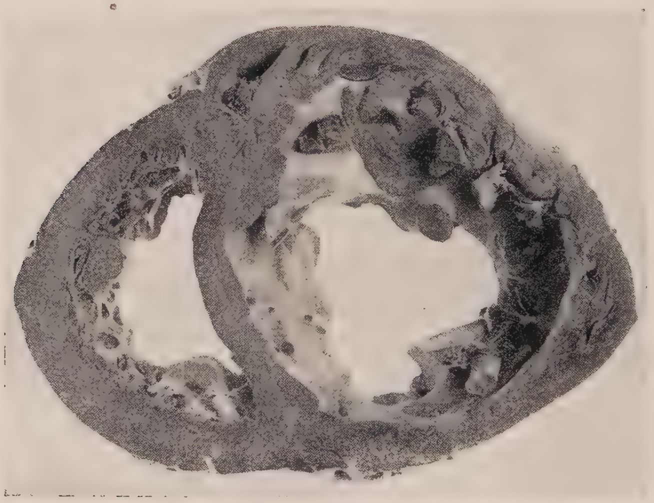

Fig. 237.—Transverse Section of the Ventricles in a case of Mitral Stenosis, showing the comparatively small left Ventricle and the greatly enlarged and hypertrophied right Ventricle. × $\frac{2}{3}$.

distinct murmur over the precordia, sometimes also to a palpable thrill, during the auricular systole ; the murmur is thus known as *auricular systolic* (A. S.) or *presystolic.*

Mitral incompetence, according to the principles above explained, causes a condition which necessitates a larger left ventricle in order to pass on the usual amount of blood. The left ventricle accordingly becomes enlarged, and its wall somewhat hypertrophied, though these changes are usually of slighter degree than in the case of aortic regurgitation. From the outset there are dilatation of the left auricle and engorgement of the pulmonary circulation. Increased work is thrown on the right ventricle, which becomes hypertrophied and enlarged. The subsequent effects are similar to those occurring in mitral stenosis. Lesions affecting primarily the valves on the right side of the heart, which are relatively uncommon, cause corresponding effects. Tricuspid incompetence produces enlargement of both right auricle and right ventricle, while tricuspid stenosis affects mainly the auricle. Pulmonary obstruction causes, primarily, hypertrophy of the right ventricle, but is of very rare occurrence except as a congenital abnormality.

Decompensation. In valvular disease death sometimes occurs suddenly. This is more frequent in lesions of incompetence, especially in aortic incompetence, but even in such conditions the percentage of sudden deaths is not high—not nearly so high as in myocardial disease and in lesions of the coronary arteries. Much more frequently death is the result of gradual heart failure with loss of compensation. We have spoken of the adjustment attained by hypertrophy of muscle and enlargement of cavities, by which compensation is established and the circulation may be satisfactorily maintained, though with the expenditure of greater energy than normally. Further, compensation may be attended by a certain degree of reserve power. Any physical exertion demands a greater output of blood by the heart in unit time—a greater ‘ minute-volume ’ ; and the capacity of a heart with valvular lesion to supply this of course varies greatly. As reserve power becomes less and less, the ability to meet any effort disappears and the patient can walk with comfort only on the level and slowly. Then *decompensation* may occur ; symptoms such as dyspnœa, cyanosis and œdema appear, and walking is carried on with difficulty or becomes impossible. Compensation may be restored by rest or the symptoms may go on increasing to a fatal issue. The causes of decompensation are very various. They may be in the heart itself, that is, *intrinsic*—they may be gradual, as the result of the progressive nature of a valvular lesion, or of a lesion in the cardiac muscle or in the conducting system ; again they may be sudden, as by the rupture of the cusp of a valve. The causes of decompensation may be *extrinsic* —they may be psychical in nature, a sudden mental shock, anxiety, etc. ; they may be due to indiscretions in diet, to disease in other organs, and a very common factor is the occurrence of infection such as a cold, influenza, etc. The physical condition underlying decompensation is essentially dilatation of the cavities. A cavity thus dilated acts at a disadvantage in contraction; its muscle cells are besides more or less exhausted. It fails to empty properly, and in spite of increased rapidity of action the minute-volume is decreased. The effects of secondary mitral and tricuspid incompetence become intensified; venous stagnation and œdema progress and ultimately œdema of the lungs appears. It may be added that during compensation the oxygen unsaturation of the venous blood may not be above the normal, but becomes markedly so during the stage of decompensation. When pulmonary complications such as œdema occur, arterial unsaturation becomes increased in addition.

Other Causes of Cardiac Enlargement. What may be called a physiological enlargement of the heart occurs in pregnancy, but it is of slight degree. A certain amount of hypertrophy is produced also as a result of hard physical work, athletic and military training, etc., and, as mentioned above, a temporary dilatation may occur from overstrain. Of pathological conditions outside the heart, by far the commonest and most important is increased resistance in the peripheral arterioles, as occurs in essential hypertension and in hypertension due to renal disease (Fig. 238). This leads to the most characteristic type of hypertrophy of the left ventricle—the 'concentric hypertrophy' of earlier writers. The wall of the left ventricle becomes markedly thickened, the thickness sometimes reaching 1 in., while the columnæ carneæ are enlarged and manifestly powerful (Fig. 238). The ventricle is like a cone in form, and on section the cavity is circular and surrounded by the thick muscular wall; the right ventricle, which may likewise show some associated hypertrophy, being applied to the side. The firm muscular cone of such a ventricle gives a quite characteristic impression on palpation, and is hardly met with in any other condition. The cavity of the ventricle may not be enlarged for a long period of time, but when the muscle begins to fail, dilatation follows and may become considerable; mitral incompetence, venous congestion, etc., are the common sequels. Especially is dilatation likely to occur when there is some fibrosis in

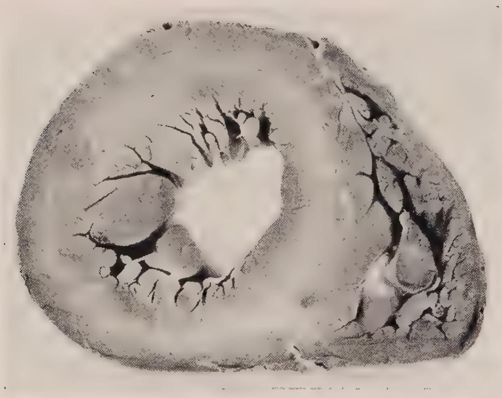

FIG. 238.—Transverse section of Heart near apex in a case of Arterio-sclerosis and Renal Fibrosis with high blood pressure.

Note great hypertrophy of wall of left ventricle. × $\frac{2}{3}$.

the myocardium, as is not uncommon in arterio-sclerosis (p. 337). As a rare cause of hypertrophy, *polycythæmia* may be mentioned. Owing to the increased number of the red corpuscles, the viscosity of blood, and thus the frictional resistance, is heightened and a certain amount of hypertrophy follows.

Another rare cause of hypertrophy of the left ventricle is *stenosis of the aorta*—a congenital lesion which occurs just beyond the origin of the great vessels from the arch (p. 368).

Adherent pericardium sometimes produces hypertrophy and dilatation of the heart, especially of the left ventricle. Not infrequently, however, we find the pericardial sac quite obliterated by adhesions, whilst the heart is not enlarged ; and it would appear that in cases of this kind, the connective tissue outside becomes stretched and loosened to such an extent that the cardiac contractions are not much affected. If, on the other hand, there is induration of the tissues owing to a spread of the inflammation, as sometimes occurs, then the systole of the heart will be interfered with, and a varying amount of hypertrophy and dilatation is the result. And there seems no doubt that adherent pericardium hampers the cardiac action to a greater degree if the heart is already enlarged, as the movement of the ventricular wall during systole is greater; thus the enlargement is further increased. Examples of very large heart are met with when there is a combination of valvular disease, especially aortic, and adherent pericardium.

Hypertrophy of the right ventricle also is caused by extrinsic conditions, namely by obstructive lesions in the lungs ; the chief of these are emphysema and chronic interstitial pneumonia, the latter lesion being either a primary one, as in silicosis, or secondary to acute pneumonia. The mode of action of these conditions in producing obstruction has been already described (p. 15). The same result follows in other conditions where there is pulmonary arteriolitis—in Ayerza's disease, occasionally in syphilis (p. 304), and in some other cases of unknown etiology. It may be added that a distinct amount of hypertrophy of the right side of the heart may be met with in cases of marked spinal curvature, with deformity and rigidity of chest due to previous rickets. In all the conditions mentioned the hypertrophy of the right ventricle may be followed by dilatation, incompetence of the tricuspid, general venous engorgement and œdema ; death often occurring with symptoms of cardiac failure. The myocardium of a hypertrophied right ventricle may be the seat of fatty degeneration and, just as occurs in mitral stenosis, patchy atheroma may be present in the pulmonary artery and its branches.

III. LESIONS OF THE CONDUCTING SYSTEM[1]

Extensive research in recent years has not only firmly established a special system of muscular tissue—the conducting system—as the means by which the impulse to contraction is transmitted from auricles to ventricles, but has demonstrated the important relations of lesions in it to morbid cardiac action. In order to make clear what follows we shall first give a short résumé of the main anatomical facts.

The conducting system or primitive muscular tissue is arranged as (*a*) two nodes—sino-auricular and auriculo-ventricular, (*b*) a bundle of fibres which takes origin from the latter, called the auriculo-ventricular bundle or bundle of His, and (*c*) the ultimate arborisations of the bundle. The *sino-auricular* or sinus node, in which the impulse to cardiac contraction starts, is an elongated and narrow structure situated in the angle formed by the junction of the superior cava and the right auricle. In addition to muscle it contains ganglionic nerve cells and plexuses, and is well supplied with blood vessels. The *auriculo-ventricular node*, a small oval body, is situated on the right side of the posterior part of the inter-auricular septum, just in front of the coronary sinus and above the attachment of the septal cusp of the tricuspid valve. It is close also to the mitral valve and may be implicated in inflammatory change extending from it. Its general structure is similar to that of the sinus node but it contains no nerve cells and only a few fibres. From it the *auriculo-ventricular bundle* passes forwards and then dips downwards in the inter-ventricular septum under the pars membranacea, where it divides into two branches, a left and a right. The left branch reaches the inner part of the left ventricle at a point on the septum corresponding with the junction of the anterior and the right posterior aortic cusp, and then runs downwards underneath the endocardium, becoming divided up into flattened branches, which ultimately end in a fine arborisation ; the fibres of the latter become continuous with the larger Purkinje fibres and these in their turn with the ordinary muscle fibres of the heart. The right branch passes downwards in a corresponding manner in the right ventricle, but is more rounded and for some distance gives off few branches. The muscle fibres of the nodes and bundle are striated, but smaller than the ordinary cardiac fibres ; they are somewhat spindle-shaped and contain much glycogen. In the nodes they are arranged in a fasciculated manner, whilst in the bundle and its branches they are arranged in a parallel fashion. The bundle and branches are enclosed in connective tissue which isolates them from the myocardium, and communicate with the ordinary cardiac muscle only through the peripheral arborisation.

As has been stated, the impulse to cardiac contraction starts in the sinus node, which is controlled by fibres from the vagus and the sympathetic. This node has, accordingly, been called the 'pace-maker of the heart.' Between it and the auriculo-ventricular node no connection by definite bundle has been found, and accordingly the impulse to the latter apparently passes through the ordinary auricular muscle. But from the auriculo-ventricular node to the muscle fibres of the ventricles, the wave of contraction follows the definite course which has been described, namely, along the auriculo-ventricular bundle, its branches and arborisations.

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[1] For a detailed account the student is referred to *Diseases of the Heart*, London, 3rd edit., 1935, by John Cowan and W. T. Ritchie, to whom I am indebted for the tracings reproduced ; and *The Mechanism and Graphic Registration of the Heart Beat*, London, 3rd edit., 1925, by Sir Thomas Lewis.

The cardiac movements and the condition of the conducting system are studied clinically by the use of two main types of instrument, viz. (*a*) the polygraph of Mackenzie or its modifications, and (*b*) the electrocardiograph. For details of their use and the results obtained, reference must be made to special works (p. 360), but we may mention some of the chief facts, especially in relation to the associated lesions.

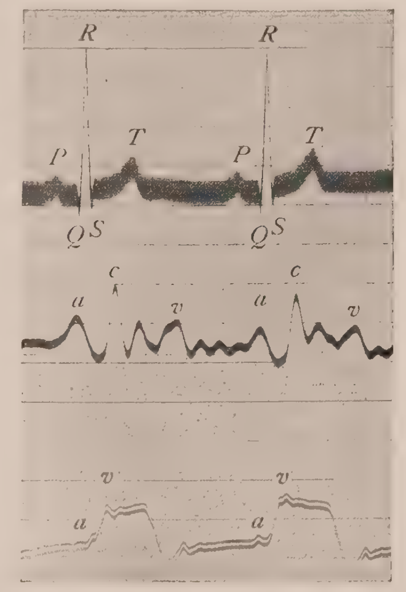

FIG. 239.—Simultaneous Electrocardiogram (Derivation II), Jugulo-Carotid Curve and Apex Impulse. Normal Heart. (C. and R.) See text for description.

The *polygraph* yields three curves, one from the right side of the neck over the venous bulb, one from the apex of the heart, and one from the brachial or other artery; there is also a time record in fifths of a second. The first or cervical curve is of most importance in connection with the conducting system and is of composite origin, being the result of movements partly from the jugular vein and partly from the underlying carotid artery. A normal tracing shows three main waves (Fig. 239). The *a* wave is venous and is due to distension of the vein as the result of auricular systole. The *c* wave is the carotid pulse, and is thus a little later in time than the commencement of the ventricular systole. The distance between the summits of the two waves, or the *a*–*c* interval, may be regarded as a proportionate representation of the time taken by the passage of the stimulus from the sinus node to the ventricles—actually it is a little more; it occupies 0·15–0·20 of a second. In the production of the third *v* wave or waves (sometimes there are two) various factors are concerned. The first part of the wave occurs during ventricular systole, and the apex corresponds with the opening of the auriculo-ventricular valves; if there are two waves the depression between them so corresponds (Cowan and Ritchie).

The use of the *electrocardiograph* depends upon the fact that a portion of muscle, as it undergoes contraction, passes into a state of electro-negativity; and, accordingly, when the active and inactive parts are made part of a circuit in which a delicate galvanometer is interposed, a minute electric current or action current is set up which can be recorded by the galvanometer. The form of electrocardiograph usually employed is that of Einthoven, which has a string galvanometer, and electrodes are applied to the hands or to one hand and one foot of the patient. The action currents produce oscillatory movements of a delicate conducting fibre, which can be photographed on a moving plate. The resulting record or electrocardiogram shows the successive phases of contraction of the cardiac muscle. In a normal electrocardiogram (Fig. 239) the wave *P* represents the small current produced by auricular contraction. The waves *R*, *S*, and *T* are due to ventricular contraction, the last occurring at the end of the systole; they together constitute 'the ventricular complex.' The distance between *P* and *R* is somewhat less than the *a*–*c* interval in the polygraph, owing to the fact that the *c* wave is really the carotid pulse, not the ventricular systole, and is of course a little later than the latter. The exact form of the electrocardiogram varies somewhat according to the manner in which the leads have been taken, and is named in conformity. In Einthoven's nomenclature, Derivation I means that the leads have been taken from the two hands; Derivation II, from the right hand and left foot; and Derivation III, from the left hand and left foot.

Disturbances of Sinus Origin. Disordered cardiac contraction is of great variety of origin, and we can attempt to explain only some of the principles on which it depends. In the first place, the impulse to cardiac contraction which, as we have said, starts in the sinus node, may be emitted at an abnormal rate or in an irregular manner, hence there arise *sinus tachycardia*, *sinus bradycardia*, and *sinus irregularity*, and these conditions depend mainly on variations in the action of the sympathetic nerves and vagi. In all these instances the events in the cardiac cycle succeed one another in the ordinary way, and the character of the condition present depends on the duration of the diastolic interval, which is shortened, lengthened, or of irregular length, according to the condition. Sinus tachycardia often represents a condition of hyperexcitability and occurs in functional nervous conditions, for example after severe physical or nervous strain, in the well-recognised irritable heart of soldiers, in neurasthenia, etc. In a state of rest the pulse rate may be only slightly raised, but it becomes greatly increased on exertion. Sinus tachycardia is met with also in disorders of the endocrine glands, especially in exophthalmic goitre, where it is part of a general hyperexcitability of the sympathetic system. In fever and in various poisonings tachycardia is of sinus origin. Sinus irregularity, which also is of functional nature and is believed to be due to variations in vagal control, occurs in similar conditions and is met with especially in early life.

Extrasystoles. Irregularities in the cardiac contractions may, however, be of quite another nature, as is shown by tracings.

Auricular fibrillation, which is described below, is an outstanding example, and one of the commonest causes is the occurrence of what are known as *extrasystoles.* This term is applied to contractions due to stimuli arising in some part other than the sinus node. An extrasystole may originate in any part of the heart—in the ventricle, auricle, or auriculo-ventricular node—the last being called a nodal extrasystole. The extrasystoles may be interspersed in an irregular manner, but sometimes ventricular extrasystoles alternate with normal contractions, the result being a coupled rhythm or *pulsus bigeminus.* Extrasystoles, unlike sinus irregularities, occur especially in the later half of life and are often due to myocardial and valvular disease, although they occur also apart from any organic lesion.

Interference with Conductivity. This is usually due to lesions of the bundle, and the effects may be of very varying degree. These have been studied by experimental methods, e.g. by compressing the bundle, as well as by clinical and pathological investigation; and it may be said that earliest evidence of interference with conduction is increase of time taken by the impulse to pass from the sinus node to the ventricles, as is shown by a lengthening of the *a–c* interval in a polygraph tracing, to more than 0·2 second, or the *P–R* interval in an electrocardiogram to a corresponding amount. Greater interference causes the occasional dropping out of a ventricular systole, the necessary stimulus failing to pass (Fig. 240), and still greater causes the blocking of stimuli in definite proportion, every second or third being thus blocked. The condition where actual blocking of some stimuli to contraction occurs, is called *partial heart block.* Finally, conduction of impulses to the ventricles may be completely stopped, the condition being then called *complete heart block.* In this condition the contraction of the auricles is determined by the sinus node, whilst the ventricles contract independently at their own rate, about 30 per minute (Fig. 241). The ventricular contractions are not affected by vagal or sympathetic stimuli and do not

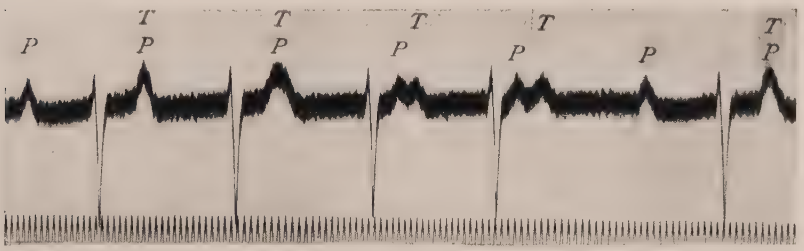

FIG. 240.—Partial Auriculo-ventricular Block.

The first *P–R* interval is prolonged (0·40 second), and successive *P–R* intervals become still longer, *P* coinciding with or preceding *T*, until the fifth auricular deflexion (*P*) is not followed by a ventricular complex. The fifth stimulus is blocked. The next ventricular complex begins 0·40 second after the sixth auricular deflexion, *P*. From a man aged sixty-one, suffering from aortic incompetence, tabes dorsalis, and diabetes mellitus. Derivation III. (C. and R.)

undergo acceleration on exertion. Heart block is sometimes associated with the *Stokes-Adam syndrome*, in which an attack of syncope or convulsions is accompanied by temporary stoppage of the cardiac contractions.

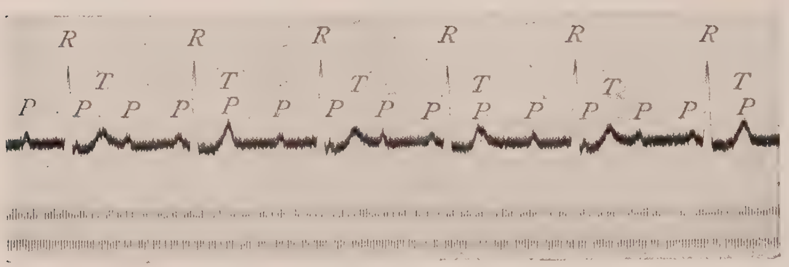

Fig. 241.—Complete Auriculo-ventricular Block.
The auricular rate is 97, the ventricular rate is 38, per minute. Derivation I. (C. and R.)

The lesions associated with heart block are of different kinds, but are mainly of a chronic character. Fibrosis (sometimes attended by calcification) which may be the result of arterial disease or of extension of inflammatory change from the base of the adjacent valves, is the commonest (Fig. 242); but also gumma, infarction or, rarely, tumour may be responsible for the interruption. Occasionally, the lesion is of acute character, such as leucocytic infiltration with partial necrosis, which has been met with especially in diphtheria; in such a case the effects may pass off. In a few cases no gross lesion has been found, and these are to be regarded in some way as functional in nature. It is known that heart block may result in some individuals from stimulation of the vagi, for example, or from the action of certain drugs, e.g. digitalis. The absence of lesion in a few cases in no way affects the established relationship of the bundle to the occurrence of heart block.

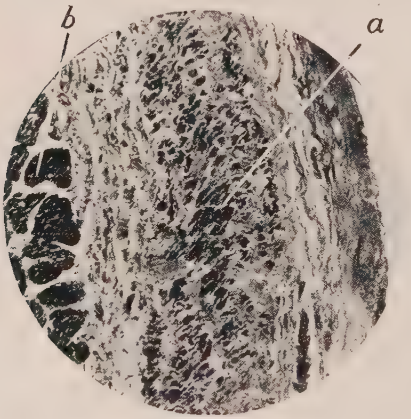

Fig. 242.—Section of Auriculo-ventricular Bundle in a case of Heart Block.
The fibres of the bundle which appear dark are largely replaced by connective tissue: *a*, fibres of bundle; *b*, ordinary muscle fibres of heart. (G. H. W.) × 45.

Auricular Fibrillation. This is a remarkable condition in which the contraction of the auricular muscle as a whole has disappeared, and instead, the muscle bundles contract independently and irregularly, so that a state of rapid quivering or fibrillation of the muscle is produced. Such a condition may be seen in the auricles of dying animals, and can be produced by faradic stimulation of the auricles. The result of the condition in the auricles is that impulses of varying force pass from the right auricle irregularly, and accordingly the ventricular contractions and the pulse waves become quite irregular. Auricular fibrillation is the cause of the irregular mitral pulse or *pulsus irregularis perpetuus*. In an electrocardiogram the ventricular rhythm is seen to be irregular, and the diastolic spaces are occupied by numerous slight oscillations due to the contraction of bundles of the auricular muscle (Fig. 243). Auricular fibrillation occurs in dilated auricles, most frequently as the result of mitral endocarditis or fibrosis of the cardiac muscle. A certain amount of irregular fibrosis is usually present in the auricular walls, and whilst some of the muscle fibres are hypertrophied, others are undergoing atrophy and disappearing. It has accordingly been supposed that the fibrillation may be due to a blocking of the conductivity at certain points, by which the contraction is deviated and irregularly distributed. In any case, it seems pretty certain that the disordered muscular contraction in fibrillation is often due to structural change in the auricular muscle.

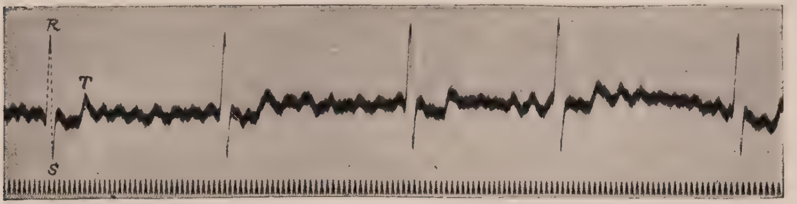

FIG. 243.—Auricular Fibrillation.

The ventricular contractions (*R*) are at irregular intervals; the small irregular waves between are due to the partial contractions of the auricles, that is, to the fibrillation (C. and R.)

Auricular Flutter. This term has been applied to a comparatively rare condition in which there are extremely rapid but regular contractions of the auricles, these numbering 250–300 or even more. In some cases the ventricular contractions are of equal number, but more frequently they are present in the proportion of 1:2, 1:3, or 1:4 (Fig. 244). The condition may appear suddenly and be of transitory character; on the other hand, it may persist unchanged for a considerable period of time. Although the condition has been observed where the heart has been apparently healthy, it occurs especially in recognisable acute or chronic cardiac disease; it has been met with also in cases of exophthalmic goitre of long standing. The rapid auricular contractions suggest some irritative condition of the sinus node, but the exact causation is not yet clear. In cases of auricular flutter, where post-mortem examination has been made, the heart has been the seat of chronic myocardial or chronic valvular disease, and the walls of the auricles have been affected by myocarditis with damage to the muscle; in some cases the sinus node has been involved, but in others it has been free from change. Although auricular flutter is a distinct condition, as shown by the fact that it may persist over months or even years, it is apparently related to auricular fibrillation and may be succeeded by the latter. And conversely, a state of fibrillation may, in certain conditions, pass into one of flutter. It is of interest to note that auricular flutter may be produced by faradic stimulation of the auricles, and that they may then pass into a condition of fibrillation.

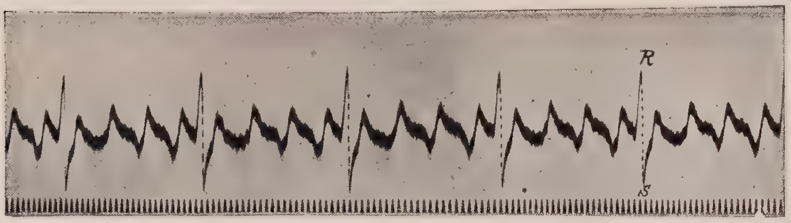

Fig. 244.—Auricular Flutter at a rate of 281 per minute, with an Auriculo-ventricular Ratio of 4 : 1. Derivation II.

From a man aged forty-five suffering from heart failure. (C. and R.)

Nodal Rhythm. In this condition the stimulus to contraction originates in the auriculo-ventricular node and then passes to the auricles and ventricles which contract almost simultaneously. When the sinus node is inhibited or otherwise thrown out of action, stimuli are produced in the auriculo-ventricular node at a slower rate than in the sinus node, and thus the nodal rhythm is associated with a certain amount of bradycardia. A corresponding clinical condition is of very rare occurrence, and is supposed to be the result of vagal inhibition of the sinus node. On the other hand, when the auriculo-ventricular node is stimulated, it may discharge stimuli at a greater rate than the sinus node and come to dominate the contractions of auricles and ventricles ; in this case the nodal rhythm is associated with tachycardia. Cases in the human subject corresponding to this latter condition are not very infrequent, the pulse rate being over 140 per minute. The features of the condition point to the existence of some irritative lesion in the auriculo-ventricular node, and such a view is supported by results of post-mortem examinations which have been made in a few cases. The node has been the seat of subacute or acute inflammatory change, and this either has spread from the adjacent mitral valve or has been part of a general myocardial affection. It might be expected that a lesion of such a kind would ultimately destroy the tissue of the auriculo-ventricular node and thus give rise to heart-block; but, so far as we know, this occurrence has not actually been met with.

CONGENITAL ABNORMALITIES

Introductory. The most important congenital abnormalities of the heart result from defects or variations in the formation of the septa in the primitive heart. For details the student must consult a work on embryology, but it may be recalled that the heart at an early stage of development consists essentially of three chambers or parts, an auricular, a ventricular, and the aortic bulb ; and that division of each of these into two takes place separately. Of special importance in this connection is the relation of the ventricular septum to the division of the distal portion of the bulb into two, which division results in the formation of the beginning of the aorta and of the pulmonary artery. The ventricular septum grows upwards from the apex, with a curved margin resulting from the growing folds on the anterior and posterior walls, until ultimately there is a relatively small aperture at the base. The bulb, on its part, undergoes division into two nearly equal parts by the formation of longitudinal folds in its wall which meet, and the two vessels formed undergo a certain amount of rotation in conformity with that of the ventricles. The septum of the bulb ultimately fuses with the up-growing ventricular septum, the last portion to close being represented by the *pars membranacea.* Important abnormalities occur in connection with the growth of these two septa. It is to be borne in mind that the position of the semilunar valves does not exactly correspond with the junction of the primitive ventricle and the aortic bulb. This is especially the case on the right side, where the lower part of the bulb becomes the upper part of the right ventricle or conus, and, as we shall see, this part is sometimes abnormally narrow. We shall first consider the chief abnormalities in connection with the formation of the different septa.

Malformations in Connection with the Aortic Bulb.—Pulmonary and Aortic Stenosis. The commonest of these result from an unequal division of the bulb, and most frequently the septum is pushed to the right, so that the aorta is abnormally large and arises partly from the right ventricle, there being usually a defect in the ventricular septum at the same time (Fig. 245). The result is pulmonary stenosis or obstruction, in the wide sense of the term, but the condition of the pulmonary artery varies. Sometimes the pulmonary artery is of small size, the division of the bulb being markedly unequal, and occasionally the small pulmonary artery is even obliterated or atresic. In other cases the narrowing is mainly at the valve, the cusps being sometimes partly fused so as to form a thickened diaphragm with an aperture of varying size. And a third abnormality occasionally met with, is a narrowing of the part of the right ventricle below the valve, that is, the part which is derived from the bulb. All these abnormalities interfere with the flow of blood into the pulmonary artery, and lead to a varying degree of hypertrophy of the right ventricle. Part of the blood from the right ventricle passes through the aperture in the inter-ventricular septum and then into the aorta, and after birth the ductus arteriosus usually remains open and the lungs receive part of their blood supply through it. The foramen ovale also remains open and may be of considerable size. *Pulmonary stenosis with septum defect* is the commonest and most important form of congenital heart lesion. Much less frequently the septum of the bulb is pushed to the left side, and then the aorta is abnormally small while the pulmonary artery is large. Such a condition also causes patency of the ductus arteriosus, but in this case the blood flows in the reverse direction, viz. from the pulmonary artery into the aorta. In this, as in other forms of congenital cardiac disease with deficient aeration of blood, there is an increase in the number of red corpuscles per c.mm. in the blood, that is, a compensatory polycythæmia. Cyanosis is often a prominent feature, hence the term *morbus cœruleus* or 'blue disease.' Owing to part of the blood from the systemic veins passing through the aperture in the inter-ventricular septum and thus not passing through the lungs, the arterial blood is imperfectly saturated with oxygen, in other words anoxic anoxæmia is present. For the reason mentioned, the cyanosis is called admixture cyanosis.

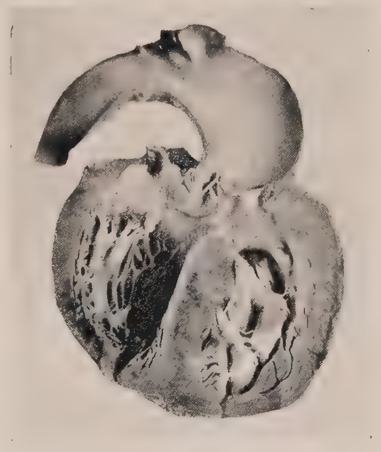

FIG. 245.—Pulmonary Stenosis due to unequal division of the Aortic Bulb.

The large aorta arises from both right and left ventricles and there is a deficiency in the ventricular septum. × $\frac{4}{5}$.

It will be readily understood that either pulmonary or aortic narrowing will cause a stream of blood from one ventricle into the other, and thus tend to interfere with the closing of the ventricular septum; and in most cases a defect in the septum is present. Sometimes, however, the septum is closed, and this will be the case when a stenosis has resulted from fœtal endocarditis after the time of completion of the septum. This type of endocarditis most frequently affects the valves on the right side. Endocarditis is, however, responsible for only a small proportion of the abnormalities of the valves, such as thickening and adhesion ; most are due to abnormality in development.

A curious anomaly results when the aortic bulb does not undergo the normal spiral twisting necessary to bring its septum into relationship with the inter-ventricular septum. The pulmonary artery, instead of rotating forward and to the right, passes in the other direction, and the result is that it comes to originate from the left ventricle while the aorta springs from the right—*transposition of the great vessels.* One would expect such a condition to be incompatible with extra-uterine life, yet in some cases the child has lived for some time, this being rendered possible by a certain amount of mixing of the blood streams through defects in the septa and through a patent ductus arteriosus.

Deficiencies of the Septa. Non-closure of the foramen ovale is of fairly common occurrence, being stated as present in about 25 per cent. of normal individuals ; the aperture varies in size but is usually quite small and often valved. There may, however, be a deficiency in the formation of the septum, and a large aperture may result, occasionally in addition to a patent foramen ovale. Such defects, even when of considerable degree, appear to have little effect on the circulation. They may occasionally be the means of allowing a portion of thrombus from a vein to pass from the right auricle into the left, in which case crossed or *paradoxical embolism* results.

The frequent association of deficiency of the ventricular septum with abnormalities at the bulb, has already been mentioned. But quite apart from these, a defect at the base of the septum may occur. Usually it is comparatively small and involves only the pars membranacea, but sometimes also the muscular part is deficient and a large aperture is present, so that the heart may be almost of trilocular type. With even such a grave defect life has been prolonged for a considerable period.

Stenosis of the Aorta. Slight narrowing of the aorta between left subclavian artery and the orifice of the ductus arteriosus, i.e. in the interval where the two main streams of the fœtal circulation cross, is not very uncommon. The stenosis is rarely marked, though cases of complete atresia of the aorta at this point have been recorded ; in such a condition the blood has been supplied to the lower parts of the body by dilatation of collaterals from the carotids and subclavians. The condition is known also as *coarctation* of the aorta, and when it has been of marked degree a difference in the volume of the pulse in upper and lower limbs has been observed. Occasionally an aneurysm has developed above a stenosis of the aorta, and also rupture of the aorta, apart from the presence of an aneurysm, has been observed.

Abnormalities of the Valves. The most important of these is stenosis, which most frequently affects the pulmonary valve. The segments may be fused into a comparatively smooth membranous diaphragm with an aperture in its centre, and it may be doubted whether such a lesion results from fœtal endocarditis, as is held by some, or represents an abnormality in development. The important effects of such a lesion have already been described. Occasionally a certain amount of stenosis occurs at the tricuspid orifice and here also there is usually absence of signs of inflammatory change. If the obstruction be sufficient to diminish appreciably the passage of blood into the right ventricle, part of the blood will pass through the foramen ovale, and there will also be a stream from the left ventricle into the right through the aperture at the base of the ventricular septum, if this has not been closed. A permanent deficiency in the septum may thus be maintained as in the case of pulmonary stenosis.

Sometimes excess or deficiency in the number of the segments of the semilunar valves may be met with ; occasionally there are four segments usually somewhat unequal in size, but, as a rule, there is no interference with the efficiency of the valve. Occasionally, on the other hand, only two segments are present, and this abnormality is more frequently met with at the aortic valve. One segment is, as a rule, somewhat larger than the other and often shows evidence of fusion of two segments; the competence of the valve may not be interfered with. It has been noted that such a valve has a tendency to become subsequently the seat of bacterial endocarditis (p. 349). Cases have been recorded in which two mitral valves have been present, but such an abnormality is of great rarity.

THE PERICARDIUM

Pericarditis. In acute pericarditis the exudate may present various characters. It may be fibrinous—*dry pericarditis.* The exudate usually appears first posteriorly round the large vessels at the base of the heart as a somewhat roughened layer, but when it becomes abundant, it forms a rough covering to the heart with irregular projections, giving rise to the so-called ‘ bread and butter ’ appearance. In other cases, the exudate is chiefly a somewhat turbid fluid—*pericarditis with effusion*; but mixed or sero-fibrinous forms also occur. Other varieties are *suppurative* and *hæmorrhagic* pericarditis.

Acute pericarditis may sometimes be the result of extension of organisms from some lesion in the vicinity, e.g. empyema, suppuration in the mediastinum; or it may arise from some ulcerating growth, e.g. of the œsophagus. In the great majority of cases, however, infection is by the blood stream. Acute pericarditis is of common occurrence in rheumatic fever, and the exudate is mainly fibrinous or sero-fibrinous; it does not become suppurative. Aschoff bodies are often to be found in the epicardium beneath the exudate, and the leucocytes in the exudate are mainly mononuclears and lymphocytes. It is not uncommon in subacute and chronic Bright’s disease, pneumonia (sometimes by direct extension), septicæmias and the various infective fevers. The suppurative type is produced chiefly by pneumococci, streptococci and staphylococci; and infection by the last is occasionally secondary to small abscesses in the heart wall. *Hæmorrhagic pericarditis* sometimes occurs in Bright’s disease and in scorbutic conditions, and it may be produced by tuberculosis or by the presence of malignant growths in the heart wall—the last being a very rare occurrence. The ordinary sequel to fibrinous pericarditis is organisation of the exudate, and adhesions with partial or complete obliteration of the pericardial sac ultimately form. Sometimes, especially in rheumatic cases, there may be repeated attacks, and great thickening of the pericardium may result. There may be also calcification in the thickened fibrous tissue. Great pericardial thickening is met with also in the condition known as polyserositis or Pick’s disease (p. 584); here also calcification may follow. The effects of adherent pericardium on the heart have been described above (p. 359).

Occasionally slightly thickened patches of opaque and whitish appearance are met with in the epicardium; they are ordinarily known as 'milk spots.' They occur especially over the anterior surface of the right ventricle and the apex of the left ventricle, also over the base posteriorly; often they are numerous and of small size, but occasionally a large area of opacity is present. Milk spots are usually ascribed to pressure over the surface of the heart and are of common occurrence in soldiers as the result of pressure of the belt of the knapsack on the chest wall, hence they are sometimes spoken of as 'soldiers' spots.' They are not uncommon also in hypertrophied hearts. Occasionally, fibrous adhesions are present over an area of thickening, and it is often doubtful whether the local pericarditis has been secondary to the thickening or has been primary. Milk spots in themselves are of no pathological significance.

Tuberculous pericarditis presents some interesting features. In the first place, it is to be noted that the pericardium and heart wall are relatively immune in cases of acute miliary tuberculosis, few or no tubercles occurring in them. On the other hand, tuberculous disease of the pericardium is not uncommon, and this is due to the fact that, in most cases, the infection spreads backwards by the lymphatics from the glands. In nearly all cases which we have observed there has been long-standing disease of the upper mediastinal glands. The affection presents varying characters. At an early stage tubercles are formed, but these soon lead to inflammatory reaction and become covered with fibrin. The disease may thus appear like an ordinary fibrinous pericarditis, and its real nature may be discovered only on microscopic examination. Then, again, caseation may occur in the exudate, and this is usually followed by much thickening of the layers of the pericardium (Fig. 246), sometimes

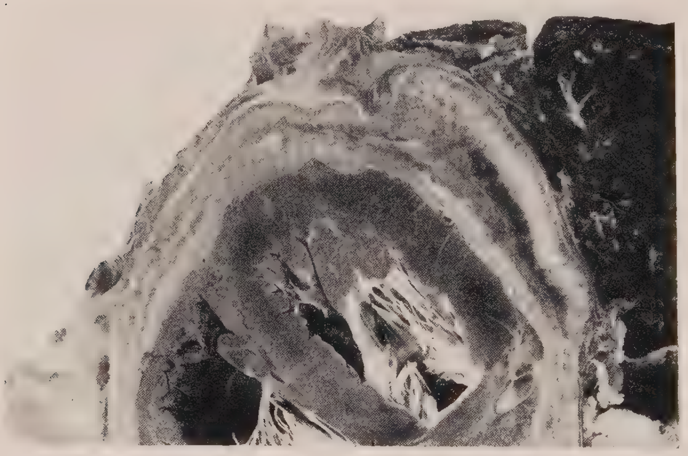

FIG. 246.—Tuberculous Pericarditis in a Child, with obliteration of Pericardial Sac and caseous change between the layers—shown on section. (J. W. S. B.)

later by calcification. In certain cases a tuberculous pericarditis at an early stage assumes a markedly hæmorrhagic character; the abundant exudate, both fibrinous and fluid, may contain a considerable admixture of blood. We have found in such a condition that the tubercle bacilli may be present in very large numbers in the exudate.

Hæmorrhage. In addition to hæmorrhagic pericarditis already described, hæmorrhage into the pericardial sac, giving rise to *hæmopericardium*, may occur in a variety of conditions. It may be due to rupture of the heart itself or to rupture of an aneurysm, or again, it may result from rupture of the aorta (p. 317) without the presence of an aneurysm. It may be produced also by a stabbing wound involving the heart or a large vessel. When the bleeding takes place rapidly, the pressure of the accumulated blood acts on the ventricles and interferes with their diastolic filling. The output of blood from the left ventricle is thus greatly diminished, the blood pressure rapidly falls and death from heart failure results. When the bleeding is more gradual a considerable accumulation of blood with passive distension of the sac may follow, and there may be little interference with the cardiac action for a considerable time.

Multiple minute hæmorrhages not infrequently occur into the layers of the pericardium in the various septic and anæmic conditions where such hæmorrhages are usually met with, and they may be due to the presence of minute abscesses in the superficial part of the heart muscle (p. 335). They are sometimes a prominent feature also in cases of death by suffocation.

Tumours of the Heart and Pericardium

Tumours of all kinds, both primary and secondary, are of rare occurrence in the heart wall. *Fibroma*, *myxoma*, *lipoma*, and *lymphangioma* have occasionally been met with; they have been observed especially in connection with the auricles, and sometimes a mass of considerable size has been present projecting into the cavity. *Hæmangioma* is another rare growth; I have recently seen one of considerable size at the upper margin of the right ventricle. *Rhabdomyoma* has been found to occur in quite a considerable number of instances. The growth, which is of congenital origin, occurs especially in the ventricles as multiple rounded nodules of pale and somewhat translucent tissue. Histologically, it is seen to consist of large branching cells in which striped fibrils are found; the cells have a somewhat vacuolated appearance and contain much glycogen. In a number of cases, of which we have met with one example, the growth has been associated with multiple discrete gliomatous growths in the cerebral hemispheres, the so-called tuberous sclerosis; sometimes there have been also malformations of the kidneys.

Metastatic growths in the heart, as we have said, are likewise very uncommon, secondary sarcoma, especially of the melanotic variety, being the form most frequently met with. The pericardium may be invaded by direct extension of growths from tumours in the vicinity, e.g. sarcoma, cancer of œsophagus or bronchi, etc. The presence of tumour growth in the pericardium is usually attended by inflammatory changes, often accompanied by hæmorrhagic exudate.

CHAPTER X

RESPIRATORY SYSTEM

Introductory. If we consider diseases of the respiratory system as a whole, it is seen that in the vast majority of cases they are initially of the nature of acute or of chronic inflammations, and of these by far the commonest cause is bacterial infection. The pulmonary tissue is in a peculiar position, as there is a direct pathway from the external air to the interior of the alveoli, and besides there is a continuity of mucous membrane from the mouth to the finest air passages along which infection may spread. Nevertheless, in the normal condition, there is a defensive mechanism by which organisms are prevented from gaining access to the lungs, and, accordingly, the alveoli and the minute bronchi are in practically a sterile condition. At what level this bacterium-free state is reached cannot be definitely stated, and no doubt it varies from time to time. But it can be readily understood how in conditions of lowered vitality the bacterial growth may extend farther downwards and set up inflammatory change. Thus in many cases, notably in bronchitis, the inflammation is produced by organisms normally present, that is *commensals*, in the mouth and upper air passages. The most striking example of this type of bacterial invasion is seen in influenza, where organisms of many kinds may invade the air passages ; but the same principle holds also in such conditions as the pulmonary complications of fevers.

In other cases, *special pathogenic bacteria* may gain entrance through the inspired air—such organisms as the tubercle bacilli, virulent pneumococci, the plague bacillus, etc., and though diminished vitality here also plays an important part in leading to infection, the presence of this may not be evident. We have mentioned that the lesion is, as a rule, initially of inflammatory nature, but this may lead to other changes ; thus, for example, chronic bronchitis ordinarily causes emphysema, which in turn causes important circulatory disturbance. The inhalation of irritating particles also may lead to pathological effects, but this is much less frequent now than formerly ; and a comparatively small proportion of pulmonary disease is caused in this way. Bacterial infection of the lungs may occur also by means of the blood stream, but this is relatively rare as compared with infection by the air passages.

The *effects* of pulmonary lesions are of two chief kinds, namely, (*a*) those arising from the infections *per se*—the growth of bacteria in the pulmonary tissue is attended with fever and the other results of absorption of bacterial products ; and (*b*) those due to interference with the functions of the lungs and the flow of blood through them. It is important to have in view those two main groups of factors, though not infrequently both are concerned. Some points may be mentioned in illustration.

(*a*) The bacterial infections vary in course and character. Some are met with as distinct diseases, whilst others, again, are secondary and often terminal phenomena occurring in other infections, notably the specific fevers. In one, namely lobar pneumonia, the disease itself has the character of a specific fever, the temperature running a definite course and terminating usually by crisis ; whilst in bronchopneumonia the fever is of non-characteristic type. The tuberculous infections are, of course, of more prolonged nature, but in them also we see the effects of absorption of bacterial toxins resulting in fever of very irregular course, wasting, etc.

(*b*) It can be readily understood how gross lesions such as œdema, collapse, pneumonic consolidation, fibrosis, etc., may interfere with the proper oxygenation of the blood. In certain parts of the lungs the blood will be circulating in the walls of air vesicles which are either filled up and do not contain air, or in which there is an imperfect movement of the air. For example, Haldane has pointed out that in the rapid shallow respiration such as is seen in lobar pneumonia, expansion of the lungs is not general and in certain parts there is little movement of the air. The general result of such conditions is that the blood returning from the lungs and passed on into the arterial system is not saturated with oxygen up to the normal amount—in other words, there is a certain degree of *anoxic anoxæmia* (p. 17). Further, if at the same time, as sometimes happens, there is an imperfect output of blood from the heart in unit of time, then venous congestion results with excess of blood in the capillaries and diminished rate of flow through them. Thus a stagnant or *congestive anoxæmia* may be produced. Both types of anoxæmia may be present together, and it is in such circumstances that *cyanosis* becomes a marked feature. We may mention lastly in this general review that certain permanent lesions in the lungs, notably vesicular emphysema and fibrosis (silicosis, etc.), diminish the total sectional area of the pulmonary capillaries and thus bring about the effects of an obstructive lesion to the blood flow. Hypertrophy of the right side of the heart and general venous congestion thus result, and death is not infrequently brought about by heart failure with its accompanying œdema, etc.

We have spoken of bacteria as the commonest infecting agents in primary disease, but there are also diseases in which filterable viruses play an important part. Epidemic influenza and coryza or the common cold are noteworthy examples. The former is often attended by severe pulmonary lesions, the latter as a rule by only trifling results, but there is similarity in the mode of action of the viruses concerned. Both viruses, entering the upper respiratory passages, lead to acute catarrh with watery secretion, and also to a lowering of the resistance of the mucosa of the passages to secondary growth of various pyogenic bacteria and to their extension down the bronchial tree. Bacterial growth is characterised by purulent secretion but it is not possible to distinguish the effects of the viruses *per se* from those of the bacteria. In the case of coryza the secondary bacterial growth was clearly demonstrated by Dochez and others by experiments both on the chimpanzee and the human subject. The pulmonary lesions in influenza are described below. It may be added that the so-called influenza bacillus of Pfeiffer is now recognised to be merely a frequent secondary invader.

LARYNX AND TRACHEA

Acute inflammations of these structures are of two main types viz. (*a*) catarrhal and (*b*) croupous or pseudo-membranous.

(A) *Acute catarrhal inflammation* is of comparatively common occurrence, and although the initial cause may be exposure to cold, irritating vapours, etc., it is mainly due to the action of bacteria which extend from the mouth and fauces. The organisms chiefly concerned are pneumococci, streptococci, and the micrococcus catarrhalis; and, in a similar way, bronchitis may be produced by a further extension of such organisms. Acute fevers and conditions of depressed vitality favour the occurrence of acute catarrh; it is accordingly specially common in measles, influenza, typhoid, etc. The naked-eye and microscopical appearances correspond with those seen in catarrhal inflammation in other parts. An acute catarrh may subside and the condition of the parts return to normal, or, on the other hand, it may pass into the chronic stage.

Chronic catarrh, which may occur without any very acute onset and is not uncommon as a result of excess in alcohol and smoking combined, is attended by important structural changes. The mucous membrane is the seat of leucocytic infiltration and new formation of blood vessels, and the connective tissue tends to become increased. Sometimes there is distinct thickening of the epithelium, which comes to be opaque in appearance; this, in the case of the larynx, may be a marked feature, and then the term *pachydermia* is applied. The mucous glands are swollen and give the surface a granular aspect, and occasionally chronic catarrh is attended by the formation of small papilliform projections.

(B) *Croupous inflammation* may, for practical purposes, be distinguished as 'diphtheritic' (caused by the B. diphtheriæ) and 'non-diphtheritic.' In *diphtheria*, the false membrane which forms on the larynx and trachea is composed mainly of fibrin and leucocytes. Columnar epithelium readily becomes desquamated, and hence the coagulated exudate rests on the basement membrane and is easily detached. In parts covered by flattened epithelium, however, e.g. the vocal cords, the membrane is somewhat adherent. Sometimes there is necrosis of the sub-epithelial tissue along with the fibrinous exudate, but this is not usual. In the case of the fauces, however, the stratified squamous epithelium becomes permeated by lymph which forms a fibrinous coagulum, whilst extensive necrosis of the epithelial cells is produced by the action of the diphtheria bacillus. The membrane has a dull, greyish-yellow colour, and is detached with some difficulty, owing to the fact that it is composed of dead epithelium firmly united with the subjacent tissues. When it is removed, the connective tissue is laid bare and bleeding-points are seen. Croupous inflammation, usually caused by streptococci, may occur apart from diphtheria. It may be set up also by the action of corrosive substances or by the inhalation of irritating vapours, notably ammonia.

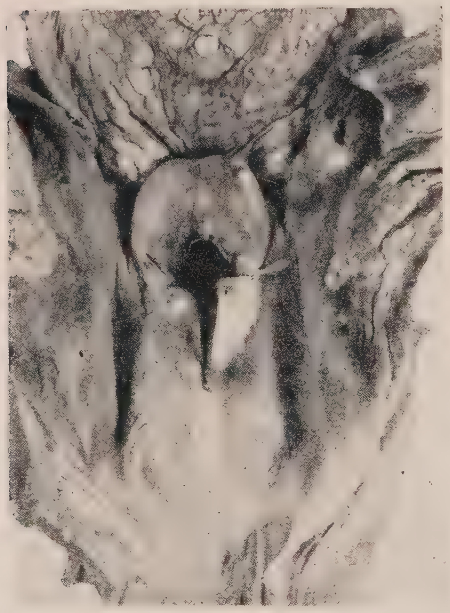

Fig. 247.—Œdema Glottidis, showing great swelling of Tissues around Orifice of Larynx.

In typhoid fever, swelling of the lymphoid tissue sometimes occurs and may be followed by ulceration, the process being analogous to that in the intestines (p. 556); the presence of typhoid bacilli has been observed in such lesions. Catarrh produced by other organisms is, however, more common in typhoid, and this also may be attended by ulceration. Occasionally the perichondrium of the cartilages becomes involved, pus forming around them, and necrosis of cartilage may follow. In smallpox, in addition to catarrhal or membranous inflammation, nodular inflammatory foci, corresponding with those in the skin, may form in the larynx and especially in the trachea. They are attended by intense congestion and hæmorrhages, but have less tendency to necrosis than those in the skin; sometimes, however, they break down and form ulcers.

Œdema Glottidis. This term is not strictly correct, as the lesion designated is an acute inflammatory œdema of the loose tissues of the upper part of the larynx and not of the vocal cords. The ary-epiglottic folds become greatly swollen and tense, and there is a similar swelling of the tissues around the epiglottis. The false cords also are affected. The lesion is an important one, as the swelling may lead to obstruction and cause death by suffocation. It is to be noted that after death the parts become less swollen and tense than they were during life. Œdema of the loose tissues mentioned may occur in cardiac and renal disease, but rarely to such an extent as to cause serious results ; the severe type is met with in other conditions. It may occur secondarily to other lesions of the larynx, e.g. diphtheria, or the deep-seated ulceration and perichondritis met with in tuberculosis, syphilis, and sometimes in typhoid. It may result also from erysipelas or from the spread of inflammation from tonsillitis and suppurative conditions in the neighbourhood ; at times from the impaction of a foreign body in the larynx. Œdema glottidis may be produced also by irritating gases, scalding fluids, etc. It occasionally occurs in angio-neurotic œdema (p. 47) and in some cases has led to a fatal result. In some of the conditions mentioned there may sometimes be an infection of the tissues by pyogenic organisms, and then a diffuse suppuration or phlegmonous condition may result, the loose tissues being then infiltrated by pus and fibrinous exudate, instead of a clear fluid as in the common condition.

The two most important *chronic infective lesions* of the larynx are those produced by tuberculosis and syphilis.

Tuberculosis. Although tuberculosis of the larynx is generally admitted to be occasionally primary, it is, in the vast majority of cases, secondary to tuberculosis of the lungs, the disease being the result of direct infection by bacilli in the sputum. The bacilli may enter the mucosa at various parts and give rise to tubercles which then become eroded and form small ulcers ; as in other places, the process of ulceration, once started, tends to spread. Any part of the larynx may be affected, but the disease often starts first and is most marked in the arytenoid region and on the vocal cords ; the ventricular bands and also the ary-epiglottic folds are common sites of ulceration. The vocal cords are not infrequently involved and their margins eaten away (Fig. 248). In a similar fashion, the epiglottis may be eroded and have an irregular outline. Occasionally, small papilliform excrescences form at the margins of the tuberculous ulcers. The disease may

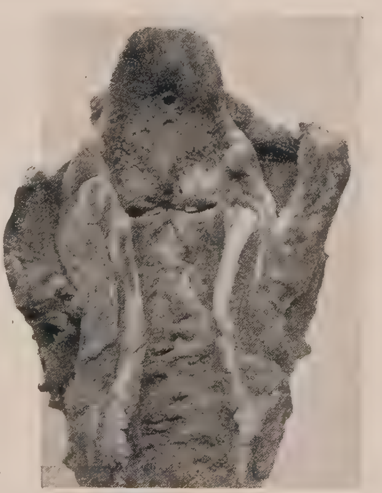

FIG. 248.—Tuberculous Disease of Larynx, showing Ulceration of Vocal Cords and also small Ulcers above and below them.

spread deeply and come to involve the perichondrium of the cartilages, especially the arytenoids, there being chronic thickening of the perichondrium attended with caseation. Ulceration may extend to such lesions, and portions of dead cartilage may be separated and discharged. These various changes are often attended by a considerable amount of inflammatory swelling; sometimes œdema glottidis is super-added. The mucous membrane of the trachea may be affected in the same way, and not infrequently a considerable number of tubercles or small ulcers may be present in cases of pulmonary tubercle. Occasionally, ulceration may extend and expose the tracheal rings.

Lupus of the larynx, although also of tuberculous nature, is quite a different condition from that just described. In the great majority of cases it occurs secondarily to lupus of the naso-pharynx, occasionally to lupus of the face. The commonest site is the upper part of the larynx, especially the epiglottis, also the ary-epiglottic folds, whilst it is unusual for the vocal cords to be involved. The disease starts in the form of small nodules or patches of thickening of a pale reddish colour, which spread slowly and undergo ulceration. Healing occurs in some places whilst ulceration extends in others, and a good deal of cicatricial contraction may result. Lupus is an indolent lesion, usually unattended by pain or secondary inflammatory change, whilst deep ulceration and involvement of the cartilages are not met with. In these respects, as well as in the conditions of incidence, it differs from the ordinary form of tuberculosis.

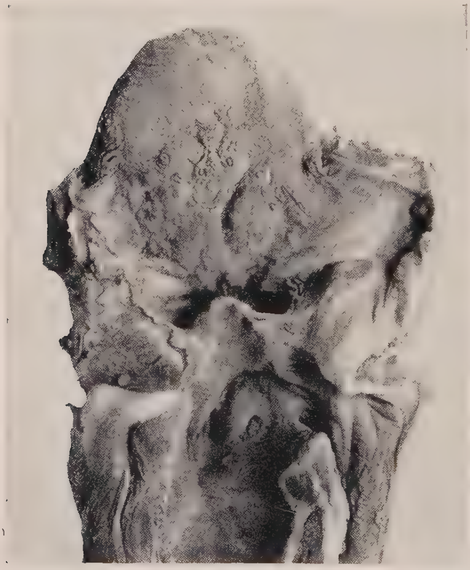

FIG. 249.—Chronic Syphilitic Disease of Larynx, showing extensive destructive change with irregular fibrosis and contraction.

Syphilis. In the secondary stage of the disease catarrh of the larynx is of common occurrence; mucous patches and superficial erosions also may be present. The most important effects, however, are met with in the tertiary stage, in which affection of the larynx is not uncommon. The lesions usually start in the submucosa of the larynx, though not infrequently in the perichondrium of the cartilages. The first change is a diffuse infiltration, which leads to irregular thickening and stiffening of the superficial parts, and often to immobility of the cartilages. This may be followed by gummatous change in the infiltrate and then by destructive ulceration. The epiglottis and other structures may thus be largely eaten away. The ulceration may extend to the affected cartilages and the latter may become necrosed and separated. What is almost a distinguishing feature of syphilitic disease, however, is a tendency to secondary overgrowth of connective tissue in the process of healing, and consequent contraction. The latter may lead to varying degrees of stenosis of the larynx, and marked deformity may result from contraction of bands of connective tissue (Fig. 249). The upper part of the trachea may be involved along with the larynx and may become narrowed, but apart from this, the commonest site of lesion in the trachea is at the bifurcation; here also ulceration with secondary cicatrisation may be met with, and not seldom the orifice of a bronchus is considerably stenosed.

Tumours. Of the simple growths those most frequently observed are the papilloma and the fibroma, the former being the commoner; angioma, myxoma, and lipoma are described, but they are very rare. Small mucous polypi and ecchondroses are occasionally met with. *Papilloma* occurs usually on the vocal cords and especially at the commissure; it is generally a single growth, but sometimes multiple. Cases have been recorded where there were numerous polypoid growths, which came to plug the larynx. When a papilloma is removed there is sometimes recurrence of growth, and sometimes malignant disease may be superadded. The *fibroma* is usually a small hemispherical growth, rounded and occasionally pedunculated. Like the papilloma, it is common on the vocal cords, and both forms of growth are apt to occur in those who use the voice much, e.g. singers.

Carcinoma is the commonest malignant growth of the larynx. In the great majority of cases it is a squamous epithelioma with little or no formation of cell-nests. It appears first in the form of a small indurated patch, not infrequently situated on a vocal cord, or there may be papillomatous upgrowth as well; in the latter case diagnosis will be unsatisfactory if only a superficial part is removed for microscopical examination. A carcinoma of the larynx presents the usual characters; it infiltrates and destroys the surrounding parts and undergoes ulceration, which is accompanied by septic infection. Not infrequently the septic discharge passes down the bronchi into the lungs and causes suppurative or gangrenous change. It may be noted that when the growth is in connection with the vocal cords it is usually less invasive, and the prognosis after removal is better, than when it arises in some other part of the larynx.

Sarcoma is much less common; it is more luxuriant in growth and presents the usual naked-eye characters. Various histological types are met with, the commonest being the spindle-cell sarcoma; lymphosarcoma also has been described.

THE BRONCHI

Bronchitis. This may be conveniently considered under the two headings of *acute* and *chronic bronchitis.* As regards both the conditions of occurrence and the effects which follow, it is important to make a distinction between acute bronchitis affecting the larger and medium-sized tubes, on the one hand, and that affecting the terminal bronchi or bronchioles, on the other—*capillary bronchitis*; though the pathological changes in the two correspond. The former is the ordinary bronchitis of the adult, and is usually a condition without serious results, unless in aged or debilitated subjects. Capillary bronchitis, however, is a much more serious affection owing to its tendency to spread and lead to pneumonia. It is comparatively rare in the healthy adult, if we except cases of influenza, as the organisms do not readily extend so low in the bronchial tree; but it is common in children and is met with also in old people. It will be described below in connection with broncho-pneumonia.

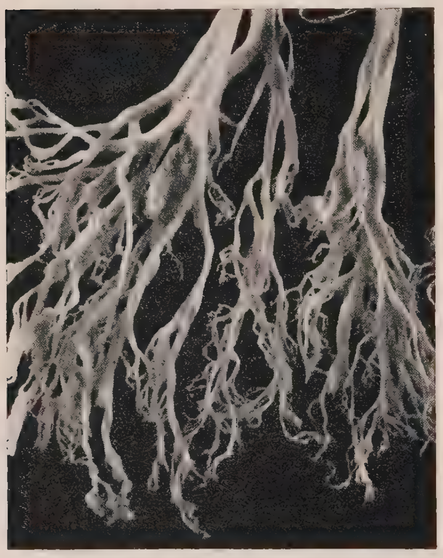

FIG. 250.—Cast of Bronchi from a case of Membranous Bronchitis.

Acute bronchitis affecting the larger tubes is usually described as of three varieties, viz. (*a*) catarrhal, (*b*) fibrinous or membranous, and (*c*) putrid bronchitis. Acute *catarrhal bronchitis* corresponds with catarrhal laryngitis so far as the organisms causing it and the exciting conditions are concerned, though it may occur with little or no affection of the larynx. The changes are essentially those of acute catarrh (p. 75). The secretion varies in character in different cases and at different stages—it may be scanty and tough, abundant and more serous, sometimes blood-stained, and in the later stages it usually becomes purulent. Complete return to normal may occur or slight catarrh may persist for some time. Chronic catarrh may result, especially when there have been several acute attacks. *Fibrinous bronchitis* is occasionally met with in diphtheria as a result of downward extension from the trachea. It may be produced by streptococci in severe fevers; and in influenza there may be fibrinous exudate in the bronchi, but usually it is scanty. There is also a chronic *membranous bronchitis,* in which abundant exudate forms on the surface of the bronchial mucosa and large casts of the bronchi may be expectorated (Fig. 250). The condition is a comparatively rare one and its etiology is unknown.

Putrid bronchitis occurs as a result of decomposition of the secretions by putrefactive bacteria. It is met with in conditions where there is stagnation of the bronchial secretion, e.g. in dilated bronchi, and in bronchiectatic cavities, and it occurs also secondarily to gangrene of the lung (p. 408). It may be set up by the passing down of fluids during narcosis or coma, and is common as a result of the ulceration of malignant growths into the trachea or bronchi. The condition is usually attended during life by abundant and highly fœtid sputum, and *post mortem* the bronchial lining shows varying degrees of greenish-brown discoloration.

Chronic bronchitis may follow acute, but is not infrequently of a chronic nature from the outset. It may result from inhalation of dust (p. 409), and it is common in cardiac disease, its occurrence being favoured by chronic venous congestion. When once chronic catarrh is established, structural changes occur in the mucous membrane, and these prevent a complete return to normal. In the mucosa there is often proliferation of connective tissue cells with formation of new blood vessels, so that the tissue is considerably increased (Fig. 251). The epithelium may be represented merely by a few pyramidal cells on the surface of the basement membrane, which may be thickened and hyaline, or there may be several layers of somewhat rounded cells. Later, these changes are followed by fibrous thickening and atrophy of all the structures ; 'hypertrophic' and 'atrophic' stages are, accordingly, described. On naked-eye examination, the bronchial mucosa is usually thickened and shows a somewhat irregular congestion. Its surface is somewhat uneven or even granular, and there is often evidence of slight dilatation of the tubes at places, notably in the intervals between the cartilaginous rings. This emphasises the transverse markings, and the longitudinal folds are more distinct than normally. The *atrophic* stage, which is

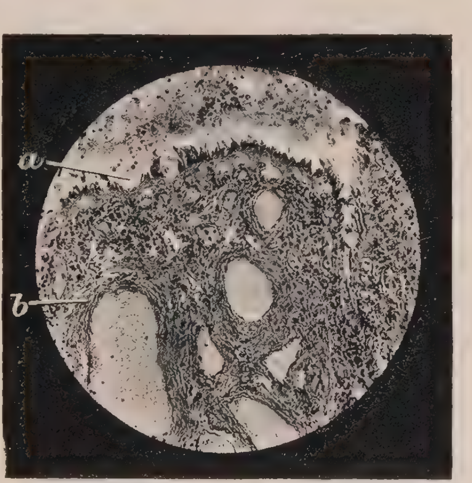

Fig. 251.—Section of large Bronchus in Chronic Bronchitis, showing (*a*) irregularity of surface and partial loss of Epithelium ; (*b*) formation of young Connective Tissue and young Blood Vessels in the Mucosa below. × 60.

less common, is characterised by general thinning of the mucous membrane. Chronic bronchitis is usually associated with vesicular emphysema of the lung, owing to the coughing which it causes (p. 388).

In *asthma*, or bronchial asthma, there occurs during the attacks a spasm of the small bronchi, and this is often accompanied by a very tough, mucoid secretion which may afterwards be expectorated. The walls of the smaller tubes in asthma have been found to be thickened, mainly owing to increase of muscle, though this is often accompanied by enlargement of mucous glands and inflammatory change. The spasmodic contraction thus occurs in tubes already narrowed. The asthmatic attack is to be regarded as an example of anaphylaxis or atopia (p. 195) due to the introduction by alimentation or inhalation of the particular foreign protein towards which the tissues have been sensitised. The increase of eosinophiles in the blood and bronchial walls corresponds with what is seen in other such states, hay fever, etc. In the sputum, eosinophile leucocytes are usually abundant, and Charcot's crystals (p. 479) are sometimes present. The sputum may contain Curschmann's spirals, which are composed of homogeneous spiral threads covered with mucin.

Bronchiectasis. By bronchiectasis is meant a dilatation of the bronchi, and this is sometimes so marked that large spaces or cavities are formed—bronchiectatic cavities. Bronchiectasis may affect bronchi in a considerable proportion of their length, and then the dilatation is of the *cylindrical* or *digitate* type. On the other hand, the dilatation may be more localised and of greater degree, so that a *sacculated* form results. Less frequently the dilatation is *fusiform*. The cylindrical type is commonest in the lower lobe, and an almost general dilatation of the tubes may sometimes be present.

Structural Changes. We have seen that in chronic bronchitis the transverse marking of the bronchial lining is often increased, and that depressions may be present between the ridges; and from this condition up to general dilatation all degrees are met with. In fully established cylindrical bronchiectasis, transverse ridging may be a prominent feature. The sacculated type is, however, usually associated with and due to a fibrosis of the surrounding lung tissue, as is described more fully below (Fig. 252). It is most frequent in the upper parts of the lung and is a not uncommon accompaniment of chronic tubercle. The lining of the bronchiectatic spaces usually resembles an irregularly swollen and vascular bronchial mucosa; it is often much congested and covered by purulent secretion, especially in the sacculated form, though at places actual ulceration may be present. On the other hand, the lining may be comparatively thin and smooth, as in the so-called atrophic form.

On *microscopic examination*, an epithelial lining may be present to a varying extent, the cells being columnar, rounded or flattened, and occurring in a single layer or in several layers; sometimes there is metaplasia to the stratified squamous type. But not infrequently the epithelium has gone, and there is a vascular and cellular granulation tissue sharply defined on the surface by what appears to be a thinned basement membrane; the blood vessels are often not only numerous but greatly dilated. Actual ulceration also may be present. The various structures of the bronchial wall—muscle, elastic tissue, glands—become atrophied and may disappear.

EFFECTS. An abundant purulent secretion is formed by the lining of the spaces, and this tends to accumulate in the dilatations and undergo decomposition. Accordingly, patients suffering from bronchiectasis often have a very abundant and foul-smelling sputum. Organisms may extend from the bronchiectatic cavities, either by the air passages or by direct ulceration, to the alveolar tissue, and pneumonia with abscess formation may be set up. Sometimes actual gangrene may occur. In such conditions the wall of a vein may become involved, septic thrombosis may follow, and this may in turn give rise to embolism and pyæmia. We have seen several cases of this nature with secondary multiple abscesses in the brain. Again, the abundant putrid secretion from the bronchi may lead to infection of the nasal sinuses and complications may thus result.

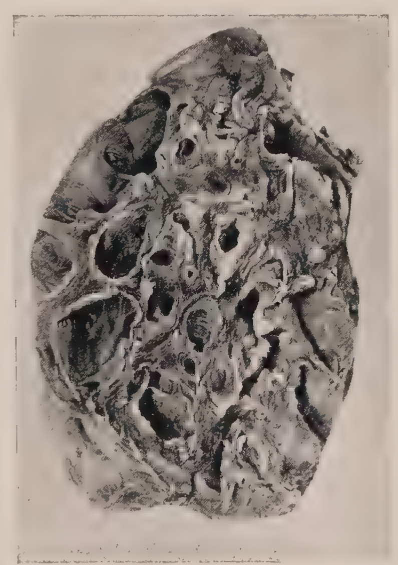

FIG. 252.—Bronchiectasis of Sacculated Type in upper Lobe of Lung.

The cavities have comparatively smooth walls and there is much fibrosis between.

CAUSATION. In the production of bronchiectasis three main factors are concerned. (*a*) In the first place there is some weakening of the supporting tissues in the bronchial wall, usually caused by inflammatory change. (*b*) The inspiratory force, especially when suddenly produced, will tend to cause expansion of any weakened parts. (*c*) The contraction of fibrous bands attached to the bronchial wall may in certain circumstances pull the bronchial wall out. It will be noted that the last two are of mechanical nature. These factors are variously combined, and all three may be present together.

(*a*) *Local weakening.* It is likely that in many cases of *cylindrical bronchiectasis* the lesion is started in early life by whooping-cough, the bronchitis of measles or of other diseases. It is noteworthy that bronchitis more readily leads to bronchial dilatation in children than in adults (Blacklock). Bronchitis of such an origin is no doubt followed by bronchiectasis in only a small proportion of cases, and in these the supporting muscular and elastic tissues of the bronchi have apparently suffered. At any rate, some general weakening of the wall seems necessary to produce cylindrical dilatation. When this occurs a vicious circle is established, the secretion tends to accumulate and the wall thus suffers further and is weakened. In the adult, influenza not infrequently leads to damage of the bronchial walls (p. 405) and may thus cause subsequent bronchiectasis, which may be localised or more diffuse. Narrowing of a bronchus may lead to accumulation of secretion in the part beyond, and thus to dilatation; but this is not of common occurrence.

(*b*) *Inspiratory force.* The chief mechanical factor is forced inspiration, especially that which follows the act of coughing; excess of air is suddenly drawn in by the negative pressure within the chest and the bronchi become expanded. This will tend gradually to produce permanent dilatation of bronchi whose walls have been previously weakened by inflammation; but it will be specially effective when the lung tissue beyond is not free to expand and receive the inrush of air. Thus atelectasis, or non-expansion of the lung after birth, and any acquired condition of collapse, are common causes of bronchiectasis. Chronic interstitial pneumonia is another fruitful cause. For example, in congenital syphilitic pneumonia where there is a diffuse fibrosis, general bronchiectasis may be present. In chronic pulmonary tuberculosis with fibrotic change bronchiectatic cavities are of common occurrence in association with the ordinary phthisical cavities; so also they are common in silicosis and fibroid conditions generally. Where there is any localised lesion of the kind mentioned the bronchiectasis tends to be of the saccular type. In all such conditions it will be readily understood how the expansile force during forced inspiration has to be borne mainly by the bronchial wall and thus the dilatation is progressive.

(*c*) *Contraction of fibrous bands.* Those attached to bronchial walls may radiate in all directions and form a connection with the pleura, which is often adherent and thickened, and thus relatively fixed. The contraction of such bands may thus pull upon the bronchial walls and tend to cause expansion of the tubes. This was the view maintained by Corrigan and is often associated with his name. We consider that this factor may play a part especially in localised bronchiectasis but is subsidiary to the previous one with which, of course, it is often associated.

A *congenital form* of bronchiectasis is met with, but it is very rare. It is characterised by the presence of cyst-like spaces in the lung, which may contain mucoid fluid. There is a corresponding non-development of lung tissue, and this has been regarded as the primary change.

Bronchiolectasis. This condition, which is of rare occurrence, is characterised by the presence of numerous small rounded spaces, rather smaller than peas, throughout the lung tissue ; the appearances are well illustrated in Fig. 253. It is difficult to recognise the exact structural relationships, but each space is apparently formed by dilatation of a terminal bronchiole and its infundibula. Small patches of chronic collapse are present, and the dilatation may be of the compensatory type ; but if this be the case it is rather difficult to understand why the presence of such spaces should be so uncommon.

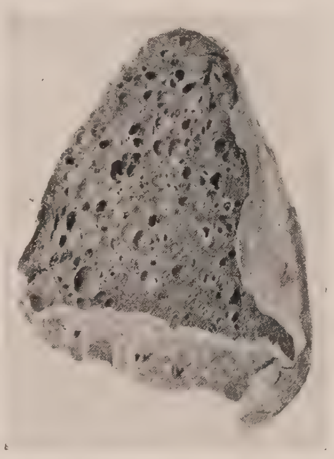

FIG. 253.—Portion of Child's Lung, showing Bronchiolectasis and Emphysema. × $\frac{2}{3}$.

Bronchial Obstruction. Various degrees of this may occur—from slight stenosis to complete closure. Either the large or the small bronchi may be affected, and the causation is somewhat different in the two cases. Obstruction of a *large bronchus* may be produced by cicatricial contraction, the commonest cause being a syphilitic lesion at the bifurcation of the trachea ; or by a tumour at the root of the lung—for example, a primary carcinoma infiltrating the wall and growing into the lumen. Obstruction may be produced also by a growth pressing on a bronchus from outside ; and a fairly common cause is aneurysm of the aorta. A foreign body lodged in a bronchus may lead to partial or to complete obstruction. When a bronchus is completely obstructed, absorption of the air in the related part of the lung occurs with comparative rapidity and pulmonary collapse is the result ; but the obstruction is usually partial at first, and then accumulation of secretion tends to occur, sometimes attended by a certain amount of bronchial dilatation. Bacterial growth, however, is the most important factor, and this sets up a purulent bronchitis in the part beyond, and then further extension to the lung substance may follow, with suppurative broncho-pneumonia as a result. This is the frequent event when a bronchus is invaded by tumour or pressed on by an aneurysm. As regards the *smaller bronchi* and bronchioles, the obstruction is usually produced by inflammatory exudate, e.g. purulent plugs in broncho-pneumonia, or by fibrinous exudate. In bronchial asthma the obstruction is due to the contraction of the walls of the bronchioles, though the presence of tough secretion also plays a part. The common result of complete obstruction of bronchioles is absorption of the contained air and collapse of the lung, which is attended with compensatory emphysema in the parts around (p. 403). If the obstruction is such that air can be sucked in and cannot be expelled, as may occur in inflammatory conditions and in asthma, then acute emphysema, inspiratory in origin, may result in the area supplied by the obstructed bronchioles. Such a condition may be recovered from when the obstruction is got rid of, but when it is oft repeated, as in asthma, structural changes result and the emphysema becomes permanent.

THE LUNGS

CIRCULATORY DISTURBANCES

Many of the chief facts with regard to these have been given in a previous chapter, but certain details are to be added.

Chronic Venous Congestion. Chronic excess of blood in the pulmonary vessels is produced by any cardiac lesion on the left side which leads to deficient passing on of the blood into the aorta (p. 15), but it is seen in most marked degree in cases of mitral stenosis ; and, as has been mentioned, in this condition it cannot be got rid of by any adjusting mechanism. In fact, the more powerfully the right ventricle contracts, the greater will be the distension of the pulmonary capillaries. In a typical example of long-standing venous congestion, the lung tissue feels coarser and tougher than normally, and it has a brownish-red tint—hence the term 'brown induration' is applied to the condition. Blood scraped from the surface also may show a brownish tint. The microscopic appearances, etc., have already been described (p. 18).

With regard to *acute congestion* of the lungs—often used as a descriptive clinical term—we know nothing definite beyond the fact that it occurs in the earlier stage of acute pneumonia.

Hypostatic Congestion and Œdema. A certain degree of hypostatic congestion is always present in the lungs *post mortem*, even when death has occurred suddenly in a healthy individual, as from injury ; the blood accumulates in the dependent parts and a certain amount of serous fluid escapes into the alveoli. But in cases where dying has been gradual, and notably in those with coma, hypostatic congestion and œdema become much more marked. Sometimes œdema alone is the outstanding feature and a large proportion of the posterior parts may be airless and water-logged. When the lung tissue is squeezed, there escapes a large quantity of more or less frothy serous fluid with little admixture of blood. Such a condition of œdema of the lungs is met with most frequently in cases of nephritis with general œdema ; though sometimes also in cardiac cases, in which it probably results from relative failure of the left side of the heart. Experimental production of pulmonary œdema has already been discussed (p. 47).

Pulmonary Embolism. Occasionally a pulmonary artery or one of the large branches becomes plugged by an embolus, the source of which is usually a thrombus in a peripheral vein or in the right side of the heart ; but we have also seen a fatal embolism produced by a large mass of crumbling vegetation from the tricuspid valve. Sudden death may result from pulmonary embolism, and this appears to be brought about by a sudden diminution of the blood supply to the left side of the heart, fatal syncope resulting ; and our experience is that one usually gets a history of the occurrence of pallor rather than of cyanosis. The conditions giving rise to pulmonary embolism and the results are dealt with on pp. 29, 40. The typical *hæmorrhagic infarctions* are seen in chronic cardiac disease, with the lungs in a condition of chronic venous congestion, and it would appear that in such conditions the collateral supply from the bronchial arteries is sufficient to distend the vessels with blood, but not to maintain the circulation ; diffuse hæmorrhage thus occurs. Though the commonest cause of such infarctions is embolism, often arising from a thrombus in the right auricular appendix, infarction may also result from thrombosis in branches of the pulmonary arteries, especially when they are affected with atheroma. Occasionally a massive thrombus may form on an atheromatous patch in a large vessel. Old pulmonary infarctions may be met with, but they are somewhat rare, as the conditions which lead to infarction are usually followed by death within a short time. The old infarctions, which are composed of necrotic and hæmorrhagic tissue, assume a brownish colour, undergo a certain amount of shrinkage, and become surrounded by fibrous tissue.

If organisms are present in the embolus which causes an infarction, suppuration may follow. This commences at the periphery, so that the infarction becomes surrounded by a pale zone of softening, and ultimately an abscess may result. The infection may be by organisms of mild virulence and is then indicated merely by localised pleurisy without any suppurative softening in the infarction.

EMPHYSEMA AND COLLAPSE

Emphysema. By this is meant the presence of small bullæ or spaces containing air. These may represent greatly distended and often confluent alveoli, or they may lie in the connective tissue of the lungs ; accordingly we have the two forms of emphysema, namely *vesicular* and *interstitial*. In the great majority of cases vesicular emphysema depends upon mechanical causes, the all-important factor being over-distension of the air vesicles. In one form, however, known as *atrophic* emphysema, the condition is caused by imperfect nutrition. Vesicular emphysema may be acutely produced or may be of chronic nature ; again, it may be general or localised.

VESICULAR EMPHYSEMA

(1) *Acute.* Acute general emphysema is sometimes seen as a terminal phenomenon, when, owing to the swelling of the bronchial

mucosa or the presence of secretion in the bronchial tubes, air cannot be expelled from the lungs though it is sucked into the lung by strong inspiratory effort. The lungs thus become over-distended and voluminous, and there may be also actual rupture of the air vesicles. Such a condition was a prominent feature in death from chlorine gas in the war (1914–18), the emphysema often being of extreme degree. Acute emphysema occurs in a similar way during an attack of asthma, the bronchial obstruction in this case being caused by contraction of the muscular coat of the bronchioles aided by tough secretion ; but as attacks recur, the permanent changes of chronic emphysema develop. In this connection, it may be mentioned that in the condition of serum anaphylaxis in the guinea-pig there is a similar contraction of the small bronchioles with resulting acute general emphysema ; and in certain points asthma corresponds with an anaphylactic phenomenon (p. 192).

Acute emphysema frequently occurs *locally* around areas of collapse, such as are produced by obstruction of the bronchioles in capillary bronchitis and broncho-pneumonia. A ring of minute bullæ can often be seen around the collapsed part, and microscopic examination shows that the affected air vesicles are overstretched, and have a rounded or oval form ; the alveolar passages also are widened. Sometimes over a considerable area collapsed lobules alternate with over-distended tissue. Such emphysema is often spoken of as compensatory, and is regarded as the result of the over-distension during inspiration, brought about by the adjacent collapse. That, no doubt, is the case, but during the course of plugging of the minute bronchioles, there will often be a stage at which air can be sucked in and not expelled, just as in acute general emphysema. When recovery takes place, acute emphysema in great measure disappears, as the collapsed areas become expanded again.

(2) *Chronic Vesicular Emphysema.* There are two varieties of this condition. In one, the emphysema is produced mechanically by overstretching and the lungs become voluminous—*ordinary emphysema* with enlargement. In the other, the condition is one of atrophy from malnutrition—*atrophic emphysema.* In the ordinary type there occurs an over-distension of the air vesicles with atrophy of their walls at places, and fusion of adjacent vesicles ; in this way air-containing spaces of considerable size are formed. It is specially of importance on account of the obstruction to the circulation which it brings about. The commonest causes are chronic bronchitis, asthma, and any chronic lesion of the lungs attended by much coughing. The presence of pleural adhesions, however, will prevent its occurrence at the corresponding site. Chronic vesicular emphysema is liable to occur in those who play wind instruments.

Structural Changes. In a typical case of chronic vesicular emphysema the lungs are very voluminous, the anterior surface of the heart being covered and the diaphragm pressed downwards. The emphysematous tissue is distended and raised above the surface, thus rounding off the sharp margins of the lung; it is paler than the rest of the lung, as less carbon pigment is present, it contains little blood and pits somewhat on pressure, owing to lack of elasticity. It has a soft, downy, almost non-crepitant feeling to the touch, and air may be passed along by pressure from one part to another, owing to interruption of the alveolar walls. On section, it shows generally a delicate structure, but spaces of all sizes may be present up to large bullæ, from the walls of which fragments of ruptured pulmonary tissue project. Emphysema is most marked at the apices and along the margins, especially the anterior borders, but in extreme cases practically the whole surface of the lungs may be affected, though the condition is always slight on the posterior aspect.

On *microscopic examination*, the lung tissue is seen to have a delicate lace-like appearance, the air spaces are large and of irregular form, and communicate with one another (Fig. 254), their walls having become thinned out and interrupted at places, while the broken portions are seen projecting into the spaces and are often bulbous at their ends. By suitable methods the elastic tissue is found to be diminished in amount and degenerated, many of the fibres being stretched and broken, or quite disintegrated into granular matter. Some of the small arteries may be seen to be obliterated and hyaline in appearance.

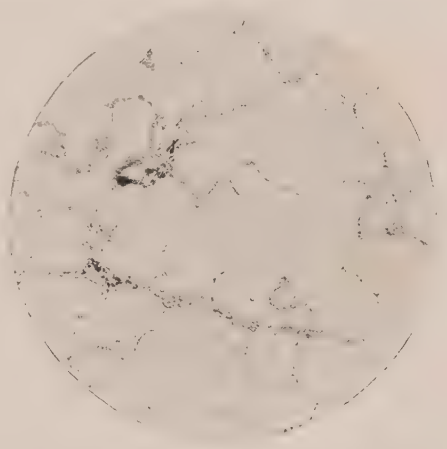

Fig. 254.—Chronic Vesicular Emphysema, showing Atrophy and partial Disappearance of Alveolar Walls. × 30.

Causation. There is no doubt that the essential factor in the production of this common type of emphysema is the oft-repeated over-distension, and that it is chiefly the result of chronic coughing. The air vesicles round the infundibular passages become distended and somewhat flattened out, and the passages are widened. The over-distension has important effects on both the elastic tissue and the capillaries. The former gradually gives way and degenerates, so that the distension becomes permanent; while, owing to the stretching of the capillaries, the blood supply of the alveolar walls is interfered with. Thus atrophic changes follow, perforations occur in the walls and enlarge, and adjacent alveoli become confluent.

These changes take place more readily in old age, where there is a tendency to atrophy, and in any condition of malnutrition.

These points seem quite clear, but there has been considerable dispute as to whether the over-distension is inspiratory or expiratory in nature. During coughing there is a powerful expiratory effort against a closed glottis, and the air within the lung is at increased pressure. Any part of the lung not sufficiently supported will be abnormally distended, and this happens at the apices, as can readily be determined by placing the fingers over the apex of an emphysematous lung during the act of coughing. But to what extent does this obtain with the rest of the lung ? It is difficult to see how the surface of the lobes where emphysema occurs, can be overstretched during the act of coughing, seeing that the increased pressure is produced not by the addition of more air to the lungs, but by contraction of the chest wall reducing the available air-space. The emphysema must occur chiefly from the over-distension which takes place from the forced inspiration which follows coughing. And, as has been indicated above, the emphysema which follows repeated attacks of asthma, is essentially the result of forced inspiration during the attacks.

Results. General emphysema has important results on the configuration of the chest and on the pulmonary circulation. The voluminous lungs lead to distension of the chest ; the ribs are raised and the sternum pushed forwards, so that the section of the thorax is more circular than normally—the characteristic barrel-shaped chest. The lungs become hyper-resonant, and the cardiac dullness disappears ; the diaphragm, with the liver, is displaced downwards. The obstruction to the flow of blood through the lungs causes hypertrophy of the right heart, and this may be followed by dilatation, etc. (p. 359). Owing apparently to increased pressure in the pulmonary arteries, atheroma is not uncommon in these vessels (p. 292), and thrombosis is sometimes met with.

A form of *localised chronic emphysema* is of common occurrence. It is found round any area of contraction or fibrosis of the lung, round puckered cicatrices or the like. Its characters correspond with those already described, and the bullæ may reach a considerable size. It is clearly produced during inspiration by over-stretching of the lung tissue around the contracted parts which are unable to expand.

Atrophic Emphysema. This is common in old age, hence sometimes called senile emphysema, but it is caused also by conditions of malnutrition, e.g. the cachexia of malignant disease, and it is often a distinct feature in pernicious anæmia. The changes are of the same nature as in the previous form, viz. atrophy of the alveolar walls, and confluence of air vesicles ; they are, however, not the result of over-stretching, but of imperfect nourishment. The change is thus a primarily atrophic one. The lungs do not become increased in size ;

on the contrary, they are usually smaller and tend to collapse when the chest is opened at a post-mortem examination. The emphysema is widespread as a rule, but is of finer character than the ordinary form; the affected tissue is soft and silky to the touch and there are no large projecting bullæ. This form usually does not lead to hypertrophy of the right heart, either because the diminished vascular area is sufficient for the needs of the body in the conditions in which the atrophic emphysema develops, or because these conditions interfere with the occurrence of cardiac hypertrophy.

INTERSTITIAL EMPHYSEMA. In this form the air is in the lymphatics of the supporting tissue of the lungs, and spreads along them. For its occurrence some laceration of the lung substance is necessary, and this may take place in two kinds of conditions, namely, (*a*) *over-distension* of the air vesicles, such as is present in severe coughing and in dyspnœa with forced inspiration, and (*b*) *traumatic laceration* of the lung tissue, produced by a portion of fractured rib or by a perforating wound. Interstitial emphysema, due to rupture of the alveolar walls from over-distension, is much commoner in children than in adults, and is met with in such conditions as whooping-cough, capillary bronchitis, and especially diphtheria of the larynx and trachea. There seems to be little doubt that the alveolar walls give way as the result of over-expansion during forced inspiration. The air is seen in the form of small bead-like collections or bullæ, usually not larger than small peas, which tend to form especially along the lines of junction of the inter-lobular septa with the pleura, thus producing a sort of reticulated arrangement on the pleural surfaces (Fig. 255). When the air is abundant, it passes by the lymphatics to the root of the lungs, and in exceptional cases it may extend even to the tissues at the root of the neck and lead to subcutaneous emphysema. Occasionally in interstitial emphysema a bulla may rupture and give rise to pneumothorax (p. 428). In traumatic emphysema the air follows a similar course, and here again there may be extension to the chest wall. We may add that we have seen interstitial emphysema as the result of severe injury to the body where there has been no fracture of ribs or wound of the lungs.

Collapse. A distinction is usually drawn between two varieties of collapse, namely a *congenital* and an *acquired*. The congenital form is really due to non-expansion of the lung tissue, and then the term *atelectasis* is properly applied, though it is sometimes used to indicate all forms of collapse. Non-expansion of the lung tissue occurs to a varying extent, especially in poorly nourished infants, and is due to muscular weakness, owing to which parts of the lung tissue fail to be expanded by inspiration. A similar cause may lead to collapse of parts which formerly contained air. Such areas of collapse are usually superficial in position and are present especially in the lower lobes. Like all areas of collapse they are somewhat depressed below the surface, and have usually a dark purplish colour owing to the non-oxygenation of the blood in the capillaries. Apart from these conditions, the two commonest causes of collapse are (*a*) *direct pressure* on the lung substance from without, and (*b*) *bronchial obstruction*, with resulting absorption of air in the corresponding area of lung tissue. With regard to the former, a lung may undergo collapse from accumulation of fluid in a pleural cavity, for example, as the result of serous effusion, hæmorrhage or empyema. In the last-mentioned condition, the collapse is sometimes very great, and the lung becomes of small size and lies posteriorly against the side of the vertebral column. When the exudate on the pleural surface becomes organised, and a 'pyogenic membrane' has formed, the lung becomes incapable of expansion to its former size, and may ultimately be enclosed by a fibrous layer; hence arises the importance of obtaining re-expansion of the lung before this happens. Collapse of a part of the lung may be produced also by direct pressure of an aneurysm or growth of any kind. The relation of *bronchial obstruction* to collapse has already been considered.

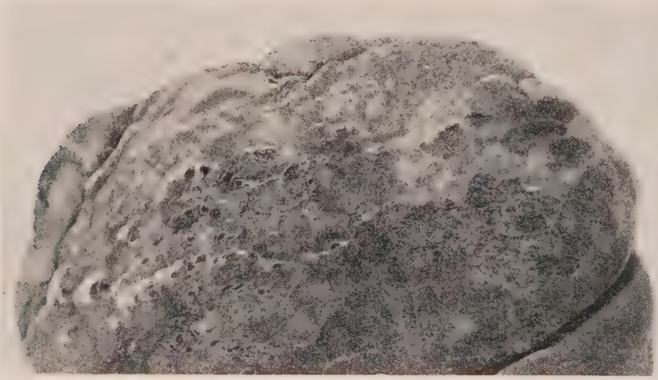

FIG. 255.—Interstitial Emphysema of Apex of Lung, showing numerous small Bullæ along the lines of Interlobular Lymphatics. (J. W. S. B.)

In a collapsed area, the walls of the air vesicles are approximated, and their capillaries are usually dilated. Owing to lack of movement of air the hæmoglobin of the blood in the capillaries of the collapsed area is largely in a reduced state—hence the purple colour on naked-eye examination. When the collapse has lasted for some time, the alveolar epithelium tends to become desquamated and an overgrowth of the connective tissue follows. This is apt to progress, and the collapsed parts become the seat of a fibrous induration which permanently prevents expansion and return to normal. Such areas of collapse and fibrosis are very often accompanied by bronchiectasis.

Acute Massive Collapse. This condition is met with most frequently after operations, especially those on the abdomen. It may occur in strong and well-nourished patients and has no relation to shock. The onset, which is comparatively sudden, is usually within one or two days after operation and is characterised by pain in the chest, dyspnœa, cyanosis and a certain degree of pyrexia. The collapse may affect a large portion of a lung, usually the right, and is commonest in the lower lobe. The chest wall is indrawn and more or less motionless, and the heart is displaced to the affected side, as is well seen in a radiogram. The condition usually passes off within a day or two, sometimes rapidly. The mechanism of collapse cannot be regarded as completely understood, but the view generally held is that it is the result of obstruction of large bronchi by tough mucus, this being probably aided by weak respiratory power. Natural relief of the condition is sometimes preceded by the expectoration of much tenacious mucus. That massive collapse can be produced by bronchial obstruction has been shown experimentally, and rapid re-expansion of the lung occurs when the obstruction is removed. It cannot be said definitely, however, that all clinical cases can be explained on this basis, and one cannot but feel doubtful whether the mode of production of massive collapse is fully understood. On the supposition that shallow respiration during anæsthesia is a factor, carbonic dioxide has been administered to stimulate the respiratory centre ; collapse, however, cannot be entirely prevented in this way.

INFLAMMATORY CONDITIONS

Acute Pneumonia

The acute inflammatory conditions of the lungs are most conveniently classified according to the mode in which the infection spreads.

(A) In one variety the inflammation starts at one place and then spreads by direct continuity, involving the various structures in its course and leading to extensive consolidation of the lung substance—*lobar pneumonia.*

(B) In another type the infection is disseminated by means of the air passages, inflammation of the minute bronchi preceding that of the pulmonary tissue. The resulting lesion is aptly termed a *broncho-pneumonia*, which varies in character according to the organisms concerned. It is called also *lobular* on account of its distribution, in contrast with lobar.

(C) Organisms may be carried by the blood stream and arrested in the pulmonary vessels, and thus give rise to inflammatory foci, which are often of a suppurative character. The term *embolic pneumonia* may be here applied. It is met with as a complication in other infections.

(D) Lastly, the accumulation of secretions in the posterior parts of the lungs may supply a medium for the growth of organisms, which set up inflammatory changes. To this variety, in which the distribution is influenced by gravity, the term *hypostatic pneumonia* is given.

(A) and (B) are the ordinary types of pneumonia occurring clinically as primary diseases.

Acute Lobar or Croupous Pneumonia. This affection has all the characters of an infective fever, and usually runs a course of about six or seven days, the fever then terminating by crisis, though sometimes the fall of temperature is more gradual. In the vast majority of cases, lobar pneumonia is caused by pneumococci, of which four types have been distinguished by workers at the Rockefeller Institute, from their serological and other characters. The recognition of these types, or 'typing,' is of great importance in connection with the serum treatment of the disease. Types I and II are responsible for the great majority of cases of typical acute pneumonia, the relative proportion varying in different places and also in the same place at different periods of the year. Type III is the *Pneumococcus mucosus*; it is relatively uncommon, but causes the most fatal form of pneumonia. It produces an exudate of a rather mucoid or glairy character; and a somewhat similar feature is noticeable in the comparatively small proportion of cases caused by the bacillus of Friedländer. Type IV includes a number of strains which are serologically distinct; it is often called 'group IV' for this reason. Pneumococci of this group are often present in the normal nasopharynx and the pneumonia caused by them is of a relatively mild character. Some further facts are given below in connection with broncho-pneumonia.

Lobar pneumonia starts usually at the base or about the root, and then spreads directly, leading to a progressive consolidation of the lung tissue. Ultimately almost the whole tissue of the lung may be involved. It resembles erysipelas both in its rapid spread by continuity, like a prairie fire, and in its rapid resolution when immunity is established. Less frequently it begins in the apex—'apical pneumonia.' The disease is usually one-sided, but occasionally it affects both lungs—double pneumonia; and when this is the case, the consolidation in one lung is more extensive than in the other, and is usually at a somewhat later stage. Lobar pneumonia is more common on the right than on the left side. The disease occurs most frequently in adult life and is comparatively uncommon in children, in whom broncho-pneumonia is the common pneumonic type.

Structural Changes. The lesion is essentially a spreading inflammation, attended usually by abundant fibrinous exudation, which leads to consolidation and an airless condition of the lung tissue. The inflammation progresses till the time of crisis; it then stops and thereafter undergoes resolution. This is the ordinary course in favourable cases, and the lung may return to a practically normal condition. In other cases, however, there follow various complications which will be afterwards described. It has been customary to describe the stages of the process under the headings of (1) *acute congestion*, (2) *red hepatisation*, (3) *grey hepatisation*, and (4) *resolution*. The first mentioned is simply a necessary stage in every acute inflammatory condition, and we may consider the appearance when exudation has actually occurred. It may be noted, however, that different parts of the same lung often show different stages of the pneumonic process.

In *red hepatisation* we find that a portion of the lung, say a lobe or more, has become consolidated or hepatised, that is, liver-like in its consistence. The affected tissue feels solid, and on section it presents on the whole a red colour, which is mottled by the presence of carbon pigment and the pale connective tissue of the lung. The cut surface is comparatively smooth or slightly granular in aspect. This appearance is due to the fact that the alveoli are filled up with a fibrinous exudate, through which the intensely congested alveolar walls can be seen. Corresponding to the area of lung affected, the earlier stages of acute pleurisy are present, the pleura being intensely congested, often showing minute hæmorrhages, and covered with a varying amount of fibrinous exudate. Fibrinous plugs may be present in the minute bronchi, and occasionally may extend into those of larger size; whilst the pleural layers between the affected lobes may be greatly swollen and glued together by fibrinous exudate. All these changes are the results of the direct spread of the pneumococci through the pulmonary tissue—the condition may be spoken of as a pan-pneumonia.

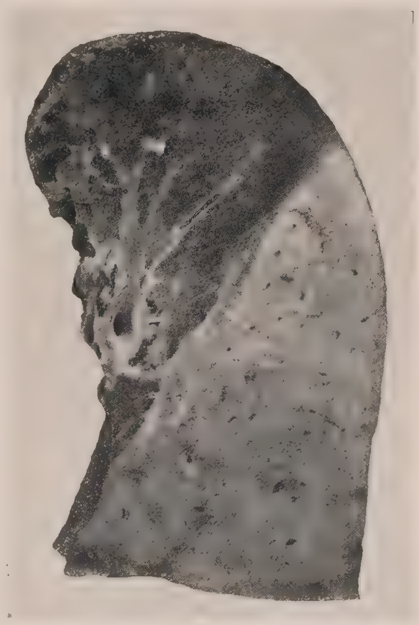

Fig. 256.—Acute Lobar Pneumonia with Grey Hepatisation in lower Lobe, Red Hepatisation in part of upper.

In the state of *grey hepatisation*, consolidation is even more complete, and the lung tissue feels denser and heavier. The cut surface shows, on the whole, a pale appearance; there is a greyish or pinkish-grey background, against which the carbon pigment of the lung stands out prominently, the appearance being aptly compared to that of grey granite (Fig. 256). The cut surface is dull and opaque and somewhat granular, and, when scraped with a knife, often gives fluid material of rather purulent aspect. The pleurisy is more marked than in the stage of red hepatisation, and the fibrinous exudate is sometimes very abundant.

At the time of crisis the pneumococci are in great part rapidly killed, the process of consolidation ceases to spread, and then in favourable cases the process of *resolution* begins. During this period there occurs a gradual liquefaction of the fibrinous exudate in the alveoli. This is shown by the fact that the consolidation is less marked, and when the lung tissue is pressed, a certain amount of fluid exudes from the surface. The process of softening or digestion of the fibrin progresses until the fibrin has completely disappeared, and thereafter the fluid within the alveoli gradually becomes absorbed and replaced by air. The process of resolution is usually to be seen at various stages. The liquefied exudate undergoes absorption by the lymphatics, though possibly in part by the blood vessels: a portion is expectorated, but in many cases the amount discharged in this way is comparatively small.

The absorption of the fibrin on the *pleural surface* is relatively slow, and the normal event is a process of organisation, which afterwards leads to fibrous adhesions between the layers of the pleura. This is apparently to be ascribed to the fact that exudate on the pleura is denser and more abundant than in the alveoli, and is also farther removed from blood vessels and the influence of leucocytes.

Some writers have questioned whether the stage of grey hepatisation really occurs in cases in which recovery follows. In connection with this, it might be said that, in a sense, there are two kinds of grey hepatisation. In the one form the inflammatory process is going on to a diffuse suppurative condition, and some of the alveoli may be seen in process of destructive softening. Where the condition has advanced so far, complete resolution would be impossible. But in all cases of pneumonia the proportion of leucocytes increases as the disease advances, whilst congestion becomes less marked; and, accordingly, in cases where the progress of the disease has been quite satisfactory, and where death has occurred from some other cause, e.g. heart failure, we may find the lung showing a grey appearance. We may therefore assume that in cases where there is recovery a grey or paler stage is the usual event.

THE MICROSCOPIC APPEARANCES need only be briefly described as they are essentially those of a typical acute inflammation. In the early stage of red hepatisation we usually find a delicate fibrinous reticulum filling the alveoli (Fig. 257), and also fibrin extending as strands between adjacent alveoli. Fibrin is present also in the septa, and the minute bronchioles may sometimes contain fibrinous plugs. Within the alveoli a varying number of polymorphonuclear leucocytes and of red corpuscles, which have escaped by diapedesis, are present in the fibrinous reticulum; and some of the cells of the alveolar epithelium, which have become swollen and desquamated, may be seen lying free. The alveolar capillaries are usually markedly congested. In some cases of lobar pneumonia, however, the fibrin is relatively scanty, the exudate being chiefly serous. In the stage of grey hepatisation, any fibrin present has undergone contraction from the walls and forms more condensed, and often somewhat granular, masses within the alveoli. There is marked increase in the number of polymorpho-nuclear leucocytes and the alveoli often appear packed with them. Some of them show signs of degeneration and many of the red corpuscles have undergone lysis and disappeared. The lung tissue has also become less congested. During the stage of resolution the fibrin becomes still more granular or amorphous in appearance, and seems to be melting away by a process of peripheral digestion. Along with the disappearance of the fibrin there occurs a gradual diminution in the number of leucocytes, these being carried off chiefly by the lymphatics, whilst there may be a considerable amount of catarrhal proliferation of the lining epithelium. Ultimately this disappears, the fluid contents and the remaining cells in the alveoli are absorbed, the epithelial lining of the alveoli is restored and the condition returns to normal. In relation to the affected lung, there occurs marked swelling of the bronchial glands, and, when resolution is going on, the lymph sinuses and paths are greatly distended, whilst in them may be seen in progress an active phagocytosis by macrophages of cells and detritus which have been absorbed from the lung.

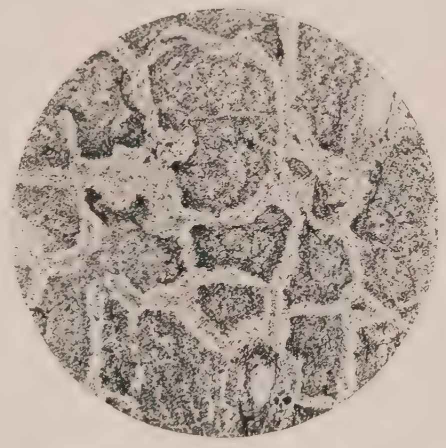

FIG. 257.—Section of Lung in stage of Red Hepatisation, showing general consolidation with abundant network of Fibrin in the Alveoli, which appears dark. (Stained by Weigert's fibrin method.) × 60.

ASSOCIATED PHENOMENA. Lobar pneumonia forms the best example of a bacterial infection running a definite course like a specific fever and terminating by crisis. The inflammatory changes in the lung tissue are attended by rapid and shallow respiration, the respiratory rate being proportionately much more increased than the pulse rate. The essential factor is a rapid and diffuse spread of pneumococci throughout the pulmonary tissue, and in accordance with the lesions the organisms are found in the interstitial tissue, pleura, etc., as well as in the contents of the air vesicles. The spread of the organisms is accompanied, however, by a process of *immunisation* with the appearance in the blood of antibodies, and when these reach a certain level the growth of the organisms is brought to an end and the crisis occurs. Were it not for this, continued growth with inflammatory change would go on and suppuration in the lung tissue would follow. This last occurrence is sometimes seen when the crisis fails to occur, as will be described below.

Throughout the stage of fever there is usually a well-marked polymorpho-nuclear *leucocytosis*, which rapidly falls at the time of crisis, being followed often by a percentage increase of mononuclears. As stated in a previous chapter (p. 77) the presence of leucocytosis indicates that the cellular defence of the body is satisfactory, and it is so far a favourable sign; but it does not signify that the patient will recover, as death may occur from various causes—heart failure, etc. On the other hand, the absence of definite leucocytosis or, when it has been established, its disappearance before the crisis, is to be regarded as indicating an excess of toxic action on the bone-marrow or want of power of response on the part of that tissue; it is therefore of grave significance.

It is an interesting fact that in some cases of pneumonia the degree of oxygen saturation of the arterial blood is up to the normal or practically so. This is remarkable in view of the fact that a large proportion of the air vesicles are out of action, and one would expect accordingly that the blood from them would return to the heart in a non-oxygenated state and thus *anoxic anoxæmia* would result. The explanation, as Haldane supposes, may be that there is very little circulation of blood through the consolidated parts. A certain amount, it would appear, must be present, as otherwise serious nutritional effects or even necrotic change would follow; and the effective distribution and action of the antibodies also demand blood flow. The whole matter seems to us of puzzling nature and requires further investigation. In other cases of pneumonia, however, anoxic anoxæmia is present, and at the same time there may be deficient output of blood from the heart and thus accumulation of blood in the venous system with accompanying congestive anoxæmia (p. 16). In such circumstances the amount of oxygen unsaturation of the venous blood may be very high and *cyanosis* may be present. When the latter is marked the prognosis is usually grave.

Complications. Whilst resolution is to be regarded as the normal termination to lobar pneumonia, it does not always occur, and we have to consider now some less favourable results or complications which may follow.

Organisation of Exudate and Fibrosis. We have already pointed out the difference between the fate of the exudate in the alveoli and that on the pleural surface. In some cases, however, digestion of the fibrin in the alveoli and absorption do not take place, and then a process of organisation occurs from the alveolar walls. It is difficult to say precisely what prevents the process of normal resolution, but in cases where organisation is beginning, one usually finds that leucocytes within the alveoli are scanty, whereas the fibrinous plugs are dense and hyaline in appearance. Probably the former phenomenon is of greater importance. In the cases in question there is proliferation of the connective tissue cells of the alveolar walls, and this is accompanied by a formation of new capillary buds and their growth into the alveoli (Fig. 258). The later stages are the usual ones of devascularisation and increased formation of fibrous stroma with contraction, the ultimate result being a fibrosis or chronic interstitial pneumonia ; to this the term *carnification* is sometimes applied. Lobar pneumonia, in fact, is to be regarded as a not infrequent cause of diffuse interstitial pneumonia (p. 409).

Suppuration. The commonest lesion of this nature is a *diffuse suppurative softening.* The lung has the characters of advanced grey hepatisation and appears comparatively bloodless, but, in addition, there are evidences of softening of the pneumonic tissue. This may be of comparatively slight degree, so that only a moderate amount of pinkish purulent material is obtained on scraping with a knife ; but in other cases considerable areas may become softened and almost liquefied. Such appearances may be accentuated by post-mortem autolytic processes, but microscopic examination shows clearly that the change is really a suppurative one, occurring during life. It is found that the alveoli are filled with enormous numbers of polymorpho-nuclear leucocytes, whilst in many parts the fibrinous exudate has entirely disappeared and the walls of the alveoli are seen to be in process of softening, so that larger spaces filled with purulent material are formed by their confluence. This process is not infrequent in cases where death has occurred about the eighth day without crisis or resolution, and may be regarded as the natural result of persistent multiplication of the pneumococci, instead of their being killed off as usually happens. Suppurative change is not uncommon in alcoholics.

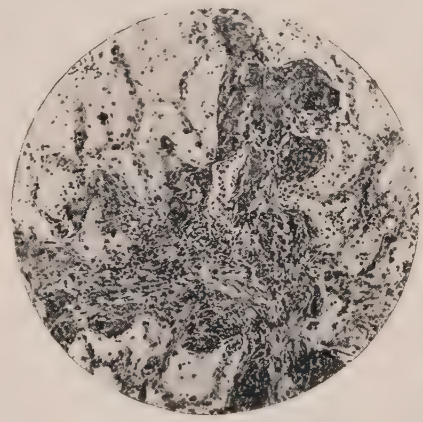

Fig. 258.—Process of Organisation in Unresolved Lobar Pneumonia, showing new formation of Connective Tissue and ingrowth into Fibrinous Masses within the Alveoli. × 80.

Localised abscesses are another occasional result of lobar pneumonia. They vary in size and number and are surrounded by the consolidated lung tissue. It is not always possible to say how they originate, but sometimes they arise in connection with some preexisting local lesion, for example, bronchiectasis. Occasionally they become chronic and perforate into the pleural cavity.

Gangrene of the Lung (p. 408). This is a rare complication and is due to the secondary invasion of the pneumonic tissues by putrefactive organisms. It is met with sometimes in diabetic patients, in alcoholics, and in others whose resisting powers are markedly diminished; it occurs also sometimes in the pneumonia following influenza. A rapidly fatal result follows in the great majority of cases.

OTHER COMPLICATIONS. In addition to the various results in the lung, pneumococcus infection may ensue in other parts. Sometimes the pneumococcus extends to the pericardial sac and sets up *pericarditis*, and this takes place more frequently when the pneumonia is on the left side. The exudate may become purulent in character. *Empyema* is another complication, which is met with, however, more frequently in children than in adults. In cases of pneumonia, the pneumococci pass into the blood stream, and in severe cases may be present in considerable number, so that various degrees of septicæmia result. The organisms may then settle in different parts of the body and give rise to inflammatory change. The soft membranes of the brain are not infrequently invaded, and the resulting lesion found *post mortem* may vary from an intense congestion to a *meningitis* with abundant greenish-yellow and semi-purulent exudate. Another complication is infection of the heart valves, and the *bacterial endocarditis* which results is often characterised by the formation of large crumbling vegetations. Acute *arthritis* occasionally occurs as a sequel to pneumonia, but it is rare.

Broncho-pneumonia. Taking as the characteristic of this condition a spread of inflammatory change from the terminal bronchioles to the alveoli, as explained above, we may say that there are several varieties, the chief of which are the three following:

(A) In the first place there is the ordinary or *simple* (*non-suppurative*) *broncho-pneumonia*, a condition in which there is pneumonic consolidation of lobular or patchy type, and in which, as in lobar pneumonia, resolution may follow.

(B) We may recognise in the second place a *suppurative or septic broncho-pneumonia*, where the consolidation is followed by suppuration and the formation of groups of abscesses, which may become confluent. Sometimes gangrenous change may be present, so that we may speak of *gangrenous broncho-pneumonia*.

(C) *Tuberculous broncho-pneumonia*. This is a condition in which the tubercle bacilli become disseminated by the air passages and in which the pneumonic change is succeeded by caseation.

It will be noted that while in the first type resolution may occur, in the second two types this is not possible, as there is actual destruction of lung tissue.

Simple Broncho-pneumonia—Non-suppurative. This occurs especially in childhood, is a common and serious complication of whooping-cough and measles, and is not infrequent in scarlet fever and diphtheria. It is met with, however, apart from these diseases, and is, especially in poorly nourished children, a comparatively fatal disease.

In connection with this subject it is to be noted that the bronchial mucosa of the adult has much greater resistance to bacterial invasion than that of the child, and that in the healthy adult it is comparatively rare for a descending infection to extend to the alveoli and cause broncho-pneumonia. In old age, however, the liability to broncho-pneumonia again occurs. When the resisting power is lowered by other infections, e.g. typhoid fever, broncho-pneumonia is not uncommon in the adult; but the outstanding example of this is seen in influenza, where it is met with as the ordinary pulmonary lesion. Further, it may be caused by the inhalation of irritating gases. Simple broncho-pneumonia is usually caused by the pneumococcus and there are comparatively few cases in which this organism is not present. It may be produced by other organisms, such as streptococcus, micrococcus catarrhalis, meningococcus, etc., whilst in the influenzal type, the influenza bacillus is usually present in large numbers. The diphtheria bacillus and typhoid bacillus may be met with in the respective diseases along with the pneumococcus or other organisms.

According to Blacklock's results in Glasgow, about 90 per cent. of cases of *broncho-pneumonia* in young children are due to pneumococci, the figure being rather below this in the primary form and rather above it in the cases secondary to measles, etc. The pneumococci chiefly belong to group IV, and this is especially so the younger the child. The latter fact suggests that in very young children the broncho-pneumonia is an auto-infection. *Lobar pneumonia* is very rare in the very young, less rare in older children; it may be produced by group IV pneumococci as well as by the other types. This is in contrast with the lobar pneumonia in the adult, which is nearly always produced by the fixed types I and II (p. 394). The difference between the prevalent forms of pneumonia in the child and adult (broncho-pneumonia and lobar pneumonia respectively) cannot, however, be explained purely on the basis of the type of the organisms; apparently different degrees of susceptibility are also concerned.

In all cases the initial lesion is an acute inflammation of the minute bronchioles, that is, a *capillary bronchitis*, which afterwards extends to the alveoli. Many of the bronchioles become plugged with purulent exudate, and, as a result, the air vesicles in relation to them may undergo collapse. This is in all probability brought about simply by absorption of the contained air from the vesicles. The occurrence of collapse is often attended by emphysema, so that depressed areas of the lung are surrounded by a ring of over-distended vesicles or small emphysematous bullæ. The collapsed areas may afterwards be the seat of catarrhal change, but in most parts the inflammation spreads to the alveoli without the previous occurrence of collapse.

Structural Changes. In the stage of capillary bronchitis there is little change to be seen on naked-eye examination. The lung tissue is usually congested, and when it is squeezed small purulent drops exude from the minute bronchi. The presence of collapse is shown by portions of the lung tissue being depressed below the pleural surface and having a dark purplish colour. Such areas may be small or may be of considerable extent; around their margin on the pleural surface minute emphysematous bullæ are often visible. Broncho-pneumonia usually attacks both lungs, though one may be much more affected than the other. The change tends to occur earlier and to be more advanced in the lower lobes and in the posterior parts of the lung, but exceptions to this are met with. The implication of the lung tissue is shown by the appearance of numerous patches of consolidation which can be felt to be almost airless. Their size and colour vary. At first they are minute and tend to be red, and often they can be felt more readily than seen; later they become larger and paler, sometimes almost of grey appearance. They are arranged in groups and their margins are somewhat ill-defined; they may be interspersed amongst the collapsed parts, as already explained. As the condition advances, the pneumonic areas enlarge and become confluent, and sometimes a considerable proportion of the lung may be consolidated. Occasionally the consolidation may be almost as complete as in lobar pneumonia, but the consolidated areas have always a patchy appearance, some parts being paler than others. Moreover, in the less affected parts the lobular distribution can be quite easily recognised. A certain amount of pleurisy is usually present over the affected lung; there may be little more than a dimming of the surface, or there may be a distinct fibrinous exudation.

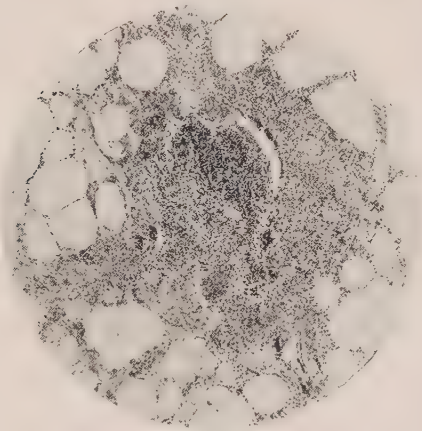

Fig. 259.—Capillary Bronchitis and Peribronchitis.

A minute bronchus is shown which has partly lost its epithelium and is filled with a purulent plug; emphysema is present around. × 50.

Microscopical Examination at an early stage of the disease shows that most of the terminal bronchioles are plugged with an exudate containing numerous polymorpho-nuclear leucocytes along with red corpuscles and desquamated epithelial cells, and sometimes sheets of detached epithelium may be seen (Fig. 259). In relation to the distribution of a bronchiole there is a collection of consolidated air vesicles, and at places it can be seen that the exudate in the bronchioles is continuous through the infundibular passages with that in the alveoli; this is, of course, an indication of the direct downward extension of the inflammatory process (Fig. 260). Spread of the inflammatory process, however, takes place in another way, viz. directly through the bronchial wall. The latter is seen to be swollen and extensively invaded by leucocytes, and it is usually surrounded by a ring of consolidated alveoli (Fig. 261). The inflammatory process here shows evidence of being fairly severe, and the air vesicles around not infrequently contain fibrinous plugs (Fig. 262). Apart from this situation, fibrin formation is uncommon in broncho-pneumonia. Whilst in a consolidated patch near a bronchiole most of the cells are polymorpho-nuclear leucocytes, at the margins where the reaction is less intense the air vesicles may contain numerous large rounded cells, which are usually regarded as being desquamated epithelial cells, though some may be macrophages which have come from the supporting frame-work. In the intervening parts of the lung many of the air vesicles may be in a condition of acute emphysema, being stretched and oval in form (Fig. 259). In other parts, as explained, the air vesicles are huddled together or collapsed and are usually markedly congested; commencing catarrh may be present in their interior.

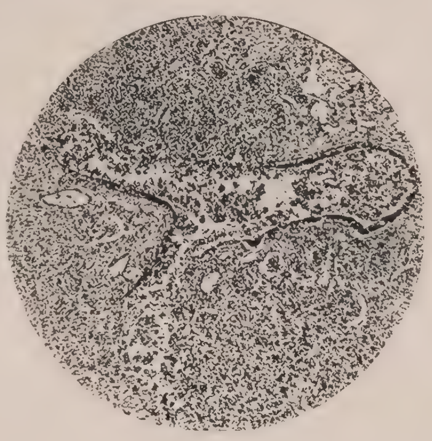

Fig. 260.—Broncho-pneumonia, showing a Terminal Bronchiole in a condition of Acute Catarrh, with spread of the inflammatory change to the air vesicles beyond. × 50.

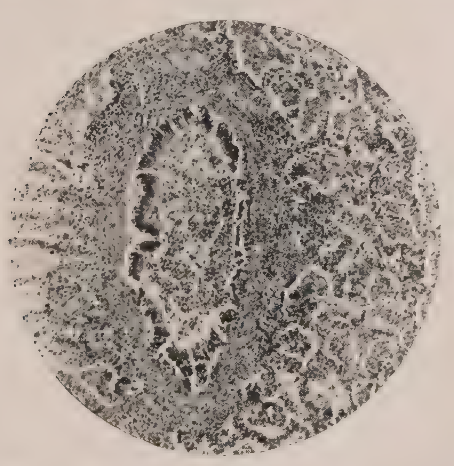

Fig. 261.—Broncho-pneumonia, showing acute Catarrh of Bronchiole with Consolidation of Alveoli around. (G. H. W.) × 60.

It is to be noted that in broncho-pneumonia cellular infiltration of the bronchial walls and interstitial tissue is usually a marked feature.

Results of Broncho-pneumonia. The natural result when recovery takes place is, as in the case of lobar pneumonia, resolution with absorption of the inflammatory exudate; but in broncho-pneumonia this is a more protracted process as there is no distinct crisis, no period at which the growth of the organisms comes abruptly to an end, and not infrequently the lung tissue does not return completely to normal. The occurrence of peribronchitis has been mentioned, and this may be followed by an overgrowth of connective tissue, which is sometimes in a nodular form, sometimes of a more diffuse character. Thus a certain amount of fibrosis may be left, and this may occasionally be attended by bronchiectasis, especially of the smaller tubes. Actual suppuration may sometimes occur in the consolidated areas, but this is not common if we except cases where there has been a passage of fluids downwards from the mouth. Empyema, usually due to pneumococci, is, however, not infrequent. Occasionally gangrenous change may take place in very poorly-nourished children, or it may be produced by the entrance of vomited material into the air passages.

Influenzal Lesions. The lesions of the respiratory passages in influenza merit special notice on account of their manifold and serious character. One of the chief effects of the virus of influenza is to lower the resistance of the respiratory tract and lead to its invasion by pathogenic bacteria of various kinds. Not infrequently the whole tract is thus invaded, and an outstanding feature is the implication of the terminal bronchioles to a degree which is not met with in any other disease in adults. The organisms chiefly concerned in producing lesions are Pfeiffer's 'influenza bacillus,' pneumococci, streptococci, micrococcus catarrhalis, and occasionally staphylococci. The trachea and large bronchi usually show signs of intense inflammation, which may be accompanied by hæmorrhage and occasionally in very severe types also by some superficial necrosis of the mucosa and some fibrinous

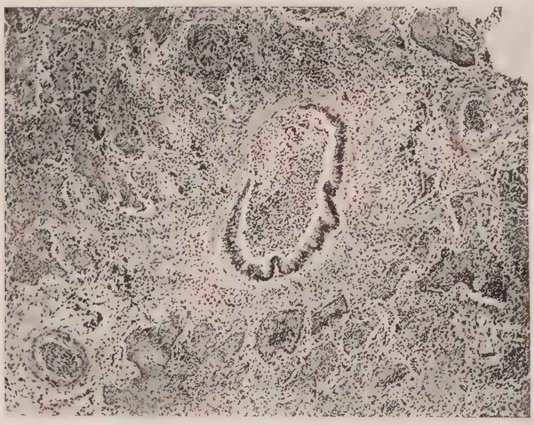

Fig. 262.—Influenzal Broncho-pneumonia, showing acute Catarrhal Inflammation of a Bronchiole and Peribronchitis.
Note the fibrinous exudate in the air vesicles around bronchiole. × 60.

exudate. When capillary bronchitis occurs, it is usually attended by intense inflammation in the vesicles around the walls of the bronchioles, often accompanied by fibrinous exudate and hæmorrhages (Fig. 262); and there is also an extension of the inflammation by way of the infundibula to the air-vesicles beyond. The walls of the tubes are the seat of marked interstitial inflammation—peribronchitis. In fact, this is a prominent feature in influenza and is of importance as it often leads to permanent fibrosis. Influenza bacilli are usually present in the exudate in the bronchi, and may be seen invading their walls, but other organisms, especially pneumococci and streptococci, are generally to be found with them. At this stage the appearance is that of an early broncho-pneumonia, but there are not infrequently hæmorrhages especially round the small bronchi, and there is usually also a considerable amount of inflammatory œdema. The areas of consolidation vary greatly in size. Pleurisy is usually present, especially when the condition has lasted some time.

Such may be regarded as the common lesions of the lungs, but various *complications* may occur. Occasionally lobar pneumonia may become superadded and may prove fatal before there is much consolidation. We have seen also cases where there was a very intense inflammatory œdema with hæmorrhage, but comparatively little consolidation, and where streptococci were abundant in the fluid exudate. The patchy pneumonic consolidation is occasionally followed by suppuration, usually in multiple foci, and the organisms may reach the pleura and give rise to an empyema. Sometimes abscesses are of chronic character and lead to much overgrowth of connective tissue. Apart from suppuration, however, interstitial pneumonia is a comparatively common sequel of influenzal pneumonia. In fact in some cases at an early stage acute interstitial inflammation is a marked lesion, and this is followed by increase of the connective tissue. Again, organisation of the exudate in the bronchioles may occur and lead to their obliteration with permanent collapse of the lung tissue beyond, and a considerable amount of fibrosis may thus result. Some small bronchi, probably as a result of damage through their muscle, undergo dilatation and thus permanent bronchiectasis may result. Occasionally in the acute stages of influenza, septicæmia, due to pneumococci or streptococci, may appear and prove rapidly fatal. This was not infrequent in the severe epidemic in 1918. The effects of influenzal infection are thus very manifold. Death may be caused by the severity of the pulmonary lesions or by septicæmia; and while the broncho-pneumonia may become resolved, recovery is often prolonged and a certain amount of fibrotic change is apt to be left.

Psittacosis. This infection, which is due to a filterable virus derived from diseased parrots, causes a form of irregular pneumonia. The lesions to the naked eye resemble somewhat those met with in influenzal broncho-pneumonia, but the exudate is stated to consist chiefly of mononuclear cells along with fibrin and red corpuscles, there being only a scanty admixture of polymorpho-nuclear leucocytes. In the oldest parts of the lesion also capillary thrombosis may be a prominent feature.

Septic or Suppurative Broncho-pneumonia. This is produced as a rule by the entrance of fluids containing pyogenic organisms into the small bronchial tubes. It is a not uncommon complication of surgical operations about the mouth or throat, and it occurs also when the bronchi become partially or completely obstructed, e.g. by tumour growth, so that secretions are retained and form a suitable medium for the growth of organisms. Occasionally it results from the presence of a foreign body in the trachea or in a bronchus. Broncho-pneumonia of similar type is met with in cases of immersion in contaminated water, a common sequel of this being suppurative and sometimes necrotic areas in the lung. The entrance of vomited material into the trachea is another cause.

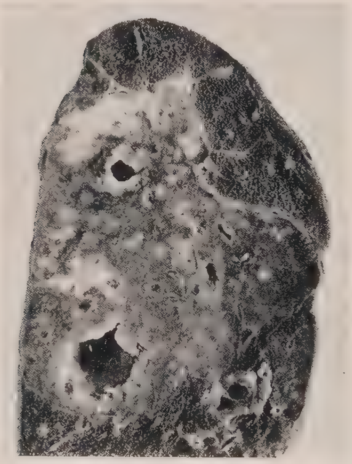

Fig. 263.—Suppurative Broncho-pneumonia, showing irregular patches of Consolidation with formation of Abscess Cavities. × $\frac{3}{4}$.

In suppurative broncho-pneumonia the consolidation occurs in patches which run together, and these afterwards undergo suppurative softening. A portion of the lung may thus come to be riddled with small abscesses, whilst a considerable amount of general pneumonic consolidation may be found between (Fig. 263). The abscesses form most frequently in the substance of the lower lobes, though they may reach the surface and infect the pleura. On the other hand, abscesses resulting from embolism are situated chiefly under the pleura. When decomposing fluids enter the bronchi, the pneumonic consolidation following may become the seat of gangrene, which sometimes produces numerous small cavities—a gangrenous broncho-pneumonia; or a large gangrenous area may result.

Tuberculous Broncho-pneumonia is described later (p. 421).

Embolic Pneumonia. In various pyæmic conditions resulting from septic invasion of peripheral veins, abscesses varying in size and number may occur in the lungs. Such abscesses were frequent in the days when surgical pyæmia was rife, but they are now much less common, and are met with chiefly in such conditions as septic thrombosis of the cerebral sinuses, and suppurative thrombosis of the uterine and other veins in puerperal conditions. They are actually suppurating infarctions and are thus often wedge-shaped. Infective emboli may be occasionally derived also from ulcerative endocarditis of the tricuspid valve. Again, in acute pyogenic infections, e.g. suppurative periostitis and osteomyelitis, there may be groups of small abscesses in the lungs, often attended by a considerable amount of hæmorrhage. In some very acute cases, especially those caused by the *Staphylococcus aureus*, the lesions may be merely in the form of numerous small hæmorrhagic areas without any actual suppuration, though some pale central points are usually to be distinguished. In the hæmorrhagic areas staphylococci may be found in enormous numbers, as plugs within the capillaries and also outside. It is important to recognise the occurrence of such a condition, as death may take place very quickly, and there may occasionally be little or no lesion in other organs to suggest the presence of the infection ; furthermore, the origin of the infection is sometimes obscure.

Pneumonic conditions may occasionally be produced by other organisms carried by the blood stream, for example in meningococcus septicæmia ; and it is possible that sometimes pneumococci may reach the lungs in this way from lesions elsewhere. In enteric fever the typhoid bacilli may be carried to the lungs by the blood, and may there take part along with pneumococci or other organisms in setting up pneumonia. In plague both types of infection are met with. In the ordinary bubonic type, secondary invasion of the lungs may take place by the blood stream, whereas in the pneumonic type infection is by inhalation. The resulting pneumonia is usually attended by much hæmorrhage and œdema, and sometimes by actual necrosis ; the bacilli are present in large numbers.

Hypostatic Pneumonia. As already stated, this type occurs from accumulation of secretions in the posterior parts of the lung, these serving as a nutrient medium for pneumococci and other organisms ; and it would appear to be an example rather of organisms of mild virulence growing under specially favourable conditions, than of virulent organisms invading the lung substance. Hypostatic pneumonia is very common in cases of coma, for example after gross cerebral lesions, also in weakly and bedridden subjects, and it is not infrequently a terminal phenomenon in cases of infective fevers. All degrees exist between a congested and œdematous condition of the lungs and true consolidation, and the lungs show corresponding appearances. The consolidation is most marked in the posterior parts of the lungs and gradually fades off in front, merging into œdema ; it is never so complete or so well-defined as in lobar pneumonia. The microscopic appearances vary much in different cases, and also in different parts of the lungs in the same case. In some cases there is chiefly catarrh, with œdema and a varying amount of hæmorrhage, whilst in others the vesicles may be largely occupied by leucocytes, and occasionally even fibrin may be present. Pleurisy is often absent, but there may be a thin fibrinous exudate at places ; there is often a certain amount of serous effusion into the pleural cavities. Hypostatic pneumonia may thus be regarded as a *terminal* affection.

Gangrene. This condition is the result of the entrance of putrefying organisms into the lung tissue, and they may reach the lung by two routes, viz. by the bronchi or by the blood stream, the former being the commoner. When infection occurs by the bronchi it usually does so by direct entrance of decomposing fluid, less frequently of solid material. This may occur in a variety of conditions—for example, during coma or as a result of operations on the tongue or larynx, in cases of ulcerating growths of these parts by the passage of discharge downwards, and not infrequently from cancer of the œsophagus, which has penetrated the trachea or a bronchus. The entrance of a foreign body, e.g. piece of carious tooth, fish bone, food, etc., may lead to gangrene. Gangrene occasionally becomes superadded to croupous pneumonia or a broncho-pneumonia, as may be met with in diabetes or in influenza. Occasionally it occurs secondarily to bronchiectasis. The gangrene is usually in multiple foci which tend to become confluent, but sometimes there is one large area involved. The tissue affected becomes softened and pulpy, of dirty brown or even greenish-black colour, and it has a highly putrid odour.

Microscopical examination shows granular material of various kinds, altered blood pigment, crystals of fatty acids, and a great variety of organisms—not only cocci and bacteria, but also leptothrix organisms, spirochætes and fusiform bacilli, etc., such as are common in gangrenous lesions about the mouth. We have seen acid-fast bacilli in gangrene of the lungs, larger and straighter than tubercle bacilli, and their presence has been noted by others.

Gangrene produced by putrid *embolism* is less common. It may be met with occasionally in cases of septic thrombosis of the cerebral sinuses, occasionally in puerperal thrombosis, the essential condition for its occurrence in all cases being the invasion of the original thrombus, not only by pyogenic, but also by putrefactive organisms. Embolic gangrene, which is sometimes in multiple foci and affects especially the superficial parts, is often in wedge-shaped areas like infarctions. Secondary pleurisy ensues, and this also may assume a putrid character.

Chronic Interstitial Pneumonia

This is characterised by an overgrowth of the connective tissue of the lungs, especially in the situations where it is most abundant, namely, around the bronchi and blood vessels, along the interlobular septa, and in the deep layers of the pleura. In this process of overgrowth the air vesicles of the lung become compressed and many of them entirely disappear (Fig. 264); whilst at places the epithelial cells lining them often assume a cubical form, somewhat resembling the cells in the fœtal lung. This is probably to be regarded as a return to an embryonic or non-differentiated type, owing to interference with the functions of the cells. Chronic interstitial pneumonia if extensive often leads to obstruction to the pulmonary circulation. Thus hypertrophy of the right side of the heart often results.

Varieties and Causation. As regards etiology, we may recognise two main types of the condition, namely:

(1) Interstitial pneumonia as a sequel to acute inflammation.

(2) Interstitial pneumonia of a chronic nature from the outset.

With regard to the first variety, it has already been described how in acute lobar pneumonia organisation of the exudate occasionally follows, and thus areas of diffuse fibrosis may result. A corresponding change is sometimes met with as a sequel to ordinary broncho-pneumonia, the fibrosis being usually patchy and sometimes attended by bronchial dilatation; whilst in the influenzal type a considerable degree of fibrosis is a not uncommon result.

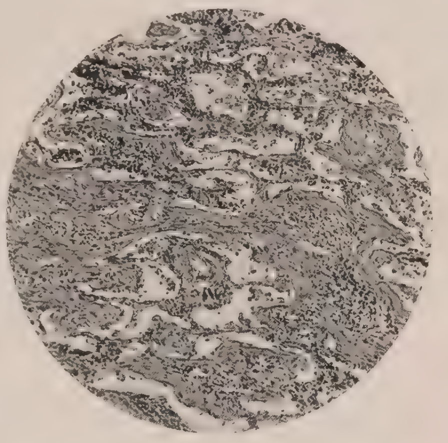

Fig. 264.—Chronic Interstitial Pneumonia, showing the increase of Fibrous Tissue in the Alveolar Walls, and obliteration of Air Vesicles. × 60.

A primarily chronic interstitial pneumonia is produced by two main causes, namely: (*a*) *inhalation of irritating particles*; (*b*) *chronic infections, especially tuberculosis and syphilis.* To the pneumonia caused by the former, the term pneumonokoniosis is given, and there are several varieties according to the nature of the substance which produces it.

Pneumonokonioses or Dust Pneumonias. These are produced by particles of various kinds, of which the commonest are coal and stone dust; also dust in potteries and pigment factories, iron particles. Lesions produced in this way were formerly common, but under improved hygienic conditions they have become much rarer. *Anthracosis* or coal-miner's lung, and *silicosis* or *chalicosis* or stone-miner's lung have long been known as the two main types in this country. Within recent times, however, another form has come to be recognised. viz. that due to inhalation of asbestos dust—*asbestosis*. The condition *siderosis*, formerly not uncommon in knife-grinders and the like, was due to a mixture of iron and stone dust. It has now practically disappeared. There is, however, another form of siderosis still met with in workers in hæmatite mines. It is to be noted that in all these types of pneumonokoniosis the important structural changes are chiefly due to silicious material.

The entrance of particles of dust into the alveoli is favoured by any abnormal condition of the bronchial mucosa, but it has been found that even when healthy animals are exposed to an atmosphere containing much dust, the particles gain access to the alveoli in a short time. They are then taken up by phagocytic cells and are carried into the lymphatics of the lung, where they become widely distributed. They tend to accumulate in certain situations, for example, along the peribronchial lymphatics and at the junction of the interlobular septa and the pleura. In the various positions where they are arrested they give rise to reactive changes, which vary according to the nature of the particles. The nature of the phagocytes in the lung alveoli has already been considered (p. 169). After the lungs have become impregnated, a reversal of the process may occur when the animal is restored to a healthy atmosphere; a certain proportion of the dust is carried by phagocytes into the alveoli and then discharged by the bronchi.

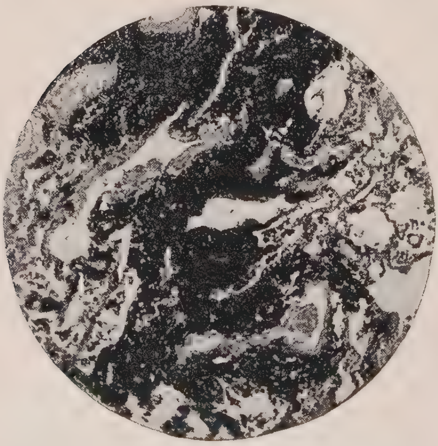

Fig. 265.—Section of Lung in Anthracosis, showing enormous accumulation of Carbon Pigment in the Tissue Spaces and Lymphatics. × 60.

Anthracosis. In all dwellers in towns there is accumulation of carbon particles in varying degree, but in coal-miners this is excessive: the whole lymphatic system of the lungs becomes impregnated and the lungs come to have an almost uniform black colour. The lungs are usually voluminous and often there is emphysema, and their texture has a somewhat coarse character, or may be even finely nodular at places. The bronchial glands are enlarged and of a jet-black colour owing to the accumulation of pigment. Occasionally fibrous masses which may be gritty are present, and these may produce ulceration into the bronchi. This lesion, however, is the result of the presence of a certain amount of stone dust in addition and is met with in coal mines where much cutting of silicious rocks has to be done. On *microscopic examination* the outstanding feature is the large amount of black pigment present in the lymphatic system; it is present diffusely and as large jet-black collections, and is attended by very little fibrous overgrowth (Fig. 265). It would seem, in fact, that carbon particles in a pure condition have very little irritating effect and do not in themselves lead to any serious damage to the lung tissue. The fibrous nodules and diffuse fibrosis which are sometimes met with, are due, we believe, to the concomitant presence of the stone dust. The general effects of anthracosis are not of a serious kind. For example, there is not the tendency to tuberculous infections which is seen in the case of silicosis. So also obstruction to the circulation is little marked, and, when it occurs, depends chiefly upon the associated emphysema.

Silicosis. This, unlike anthracosis, is a serious disease, but fortunately it is not very common. The stone particles have a markedly irritating effect and may give rise to much fibrous overgrowth. The layers of the pleura are usually adherent and thickened, and on the surface of the lung there are often scattered grey nodules of firm consistence. These occur especially at the junction of the interlobular septa and the pleura, and when cut into may be gritty to the touch. Similar nodules are present throughout the lung and larger fibrous masses may be formed by their confluence; and there is a varying degree of diffuse fibrosis of the lung substance. A certain amount of bronchiectasis is not uncommon, and there may be ulceration of the nodules into the bronchi, with formation of cavities. The lung tissue has a dark greyish colour, and, as a rule, there is also a considerable amount of carbon pigment present. Tuberculous lesions of various kinds are often present in addition. *Microscopic examination* shows that the nodules are composed of very dense connective tissue arranged in a laminated fashion, and between the fibres there are

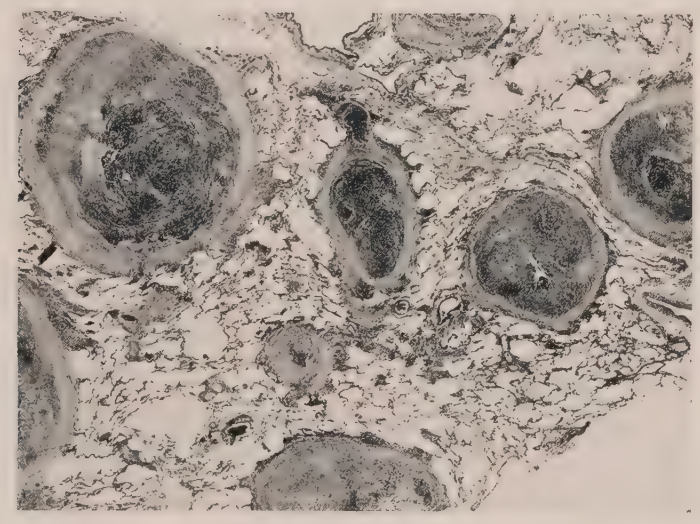

FIG. 266.—Fibrotic nodules in lung in silicosis.

Note dense laminated connective tissue. The nodules are unusually well circumscribed. (A. C. L.) × 7.

collections of stone particles which are usually very minute, somewhat angular in form and of greyish-brown colour ; their characters, however, vary according to the nature of the stone. Most of the particles are doubly refracting and are thus readily distinguished by the polarising microscope. The nodules are somewhat cellular at the periphery, whilst the central parts are more fibrous or hyaline in appearance (Figs. 266, 267). Silica has also an important action on the walls of the small arteries, and endarteritis or thrombosis may result. One may see arteries with hyaline walls and the lumen filled with organised thrombus of similar appearance, the hyaline change being here again a prominent feature. These arterial changes must have an important effect on the related nodules, the central parts of which may be practically necrotic.

Silicosis leads to serious results in two ways. (*a*) In the first place, owing to the great fibrosis and destruction or replacement of the alveolar tissue, the vascular area is diminished, and, accordingly, there is obstruction to the circulation. The right side of the heart undergoes hypertrophy, and this may be followed by dilatation, with general venous congestion and œdema as the result. The patients thus sometimes die with the signs of cardiac failure. (*b*) The other serious result is the occurrence of tuberculosis. Silicosis renders the lungs very susceptible to invasion by the tubercle bacillus, and when this occurs the lungs may be extensively involved by the two types of disease. It may be said that tuberculosis becomes superadded in more than 50 per cent of the cases. A fibro-caseous lesion is specially common amongst miners in the Transvaal. Radiography has been found of great value in ascertaining the nature of the lesions, both the nodules and the more diffuse changes being well brought out in X-ray plates.

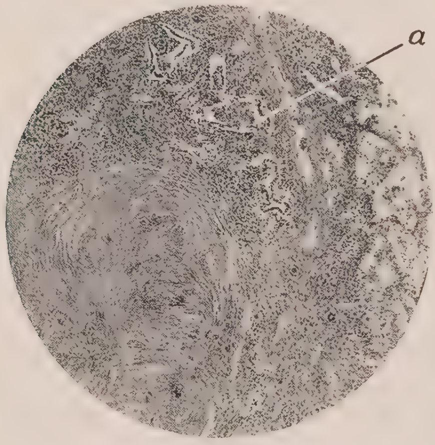

Fig. 267.—Section of Lung in Silicosis showing characteristic laminated Fibrous Nodule.

The compressed alveoli at the margin, *a*, are lined by cubical epithelium. × 60.

The facts stated above show that the action of silica is characterised by two main features, viz. (*a*) the extent of the resulting fibrosis, as contrasted with that in other pneumonokonioses, and (*b*) the susceptibility to tuberculosis which is brought about. On these two points light has been thrown by the work of Gye and Kettle. They found that the action of the stone particles on the tissues is not the result of their physical properties merely as foreign material, but is due to the slow formation of colloidal silica which diffuses around the particles and acts as an irritant and cell poison, leading to overgrowth of connective tissue and sometimes necrosis. Further, they have shown, by experimental methods, that this silica sol breaks down the defences of the tissues and leads to a more extensive growth of tubercle bacilli when they are present. In this way, the susceptibility of silicotic lungs to tuberculous infection is brought about. Their conclusions, which are well supported by the experimental results, appear to us to explain the essential features of silicosis as mentioned above. According to recent work by Denny and others, the harmful effects of silica in producing silicosis can be prevented by the inhalation of metallic aluminium powder. This action depends chiefly on the formation of a gelatinous hydrated alumina which covers the quartz particles with an insoluble and impermeable coating. It remains to be seen to what extent this result may have practical application in the prevention of silicosis.

The nature of the silicious materials concerned in the production of silicosis is still subject of enquiry but it is generally agreed that *silica* (dioxide of silicon) is chiefly responsible and that many silicates play little or no part. Recently it has been urged by Jones that the incidence of silicosis cannot be explained on the view that silica only is concerned and that sericite or secondary white mica, a fibrous silicate which occurs in very minute particles, plays an important part. This, however, is still undetermined.

Asbestosis. Within recent years this type of interstitial pneumonia has been found to be not uncommon among workers in asbestos factories. Asbestos is a fibrous silicate, the silica being combined chiefly with magnesium and iron.

The fibrosis of the lungs is of a diffuse type and is usually most marked in the lower lobes, diminishing in intensity in an upward direction ; it is often accompanied by marked pleural thickening. Accordingly, in X-ray plates the lesion presents a striated rather than a nodular appearance. On microscopic examination one finds areas of fibrosis in which the alveolar structure has disappeared, and other areas alongside in which the alveoli show an advancing fibrosis of their walls along with a varying amount of inflammatory change in their interior. The growth of tissue is often specially marked around the bronchi. Scattered in the fibrous tissue and also within the alveoli, one finds the so-called 'asbestosis bodies,' which are of great importance in the diagnosis of the disease. They are thin and of considerable length, often clubbed or bulging at the extremities and transversely fissured or notched along their length. They have a brownish yellow colour and give an iron reaction. The bodies represent asbestos filaments coated with some organic deposit from the tissues (Figs. 268 and 269). In the lung tissue they are often arranged in radiating clumps, though there are also irregular fragments of similar character, and they are accompanied by a considerable excess of carbon pigment. They have also been found to appear in the lungs of guinea-pigs within two or three months after artificial exposure to the dust. Asbestosis bodies have been found in the sputum of persons exposed to asbestos dust without there being any evidence of pulmonary lesion; their presence thus indicates merely that there has been exposure. The presence of the bodies in clumps has, however, another significance, as has been pointed out by Stewart and others. Such clumps form only in the pulmonary lesions, and their presence in the sputum would thus appear to depend on the breaking down of the tissues, either as a result of tubercle or suppurative change.

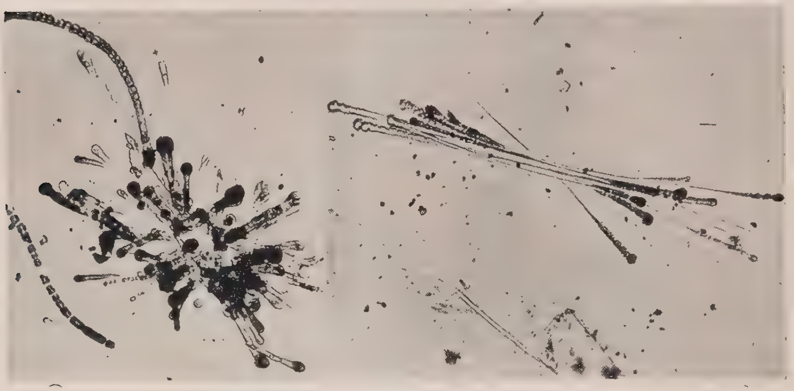

FIG. 268. FIG. 269.

FIGS. 268 and 269.—Asbestosis Bodies in Sputum from cases of Asbestosis.

FIG. 268 shows a characteristic radiating clump. × about 350.
FIG. 269 shows the process of formation by accretion of organic material around asbestos fibres. × 400. (Professor M. J. Stewart.)

There is a distinct tendency for tubercle to occur in asbestosis, though the incidence of the disease is not so high as in silicosis. Asbestosis is a very serious disease and when well established leads to a fatal result more rapidly than does silicosis. It is thus probable that there is little difference between the two diseases as regards the tendency to tuberculosis.

Pulmonary siderosis. As has been said, this may be due either to (*a*) iron or steel dust, or (*b*) oxide of iron (hæmatite). The former has now practically disappeared as a result of precautions adopted, but the latter is met with in workers in hæmatite mines and occurs in this country. The hæmatite lung is rusty brown in colour and may be extensively fibrosed. The fibrous tissue is in the form of coarse bands or is somewhat diffuse, but there are localised denser areas which may have almost a hard consistence. It is a coarser fibrosis than that of asbestosis and has not the distinctly nodular character of silicosis. Microscopic examination shows broad bands of fibrous tissue in which are few cells, and also spreading fibrosis of finer type which is of more cellular character. The hæmatite pigment is in the form of brownish yellow granules, which are abundant throughout the fibrous tissue. Most of the pigment is free and does not give the Prussian blue reaction, but a considerable amount contained within cells reacts positively. It may be added that the iron is absorbed from the lungs, probably in a colloidal state, and carried to other parts of the body, so that a varying amount of siderosis of the reticulo-endothelial system may result.

Hæmatite lungs contain a large amount of silica and this no doubt plays an important part in leading to the fibrous changes. Stewart for this reason calls the condition 'silico-siderosis'. As in silicosis, there is a marked tendency to tuberculosis.

SPECIFIC CHRONIC INFECTIONS

Tuberculosis

Of all the organs of the body the lungs are most frequently the seat of tuberculous lesions. The diversity of the lesions too is an outstanding feature and in this various factors are concerned. In the first place, an all important point is the *site of multiplication* of the bacilli. If they are in the connective tissue framework the lesion will be initially of a proliferative type with the formation of tubercles, often with secondary fibrosis; and the bacilli will spread by the lymphatics. If, on the other hand, their growth is in the air vesicles the reaction is of pneumonic type, which is soon followed by caseation. Extensive spread of the bacilli by means of the respiratory passages often occurs and leads to such a lesion. It will be readily understood how both types of lesion may be combined—how bacilli may spread from the connective tissue to the air vesicles or *vice versa*.

In any infection the feature of the resulting disease depends on the sum-total of the characters of the subject of infection, on the one hand, and of the infecting agent on the other. This is notably the case in tuberculosis; the 'soil' and the 'seed' are sometimes spoken of. Tubercle bacilli vary in virulence and their effects correspondingly vary. There is further the question of their numbers, that is, the dose. The defences of the respiratory passages may be able to deal successfully with a small number of bacilli, but if a large number are discharged into the passages, e.g. by ulceration of a caseous focus, the defences may be overwhelmed and caseating pneumonia may result.

Pulmonary tuberculosis is a disease which is strikingly affected by the general condition of the patient. States of lowered vitality, bad hygiene or the presence of other diseases, often lower the resistance and lead to the lighting-up of a dormant lesion with rapid spread of the disease. For instance, if pulmonary tuberculosis occurs in a diabetic it is usually of an acute caseating type. On the other hand, the converse conditions of favourable surroundings, etc., may have a remarkable effect in leading to the arrest of the disease and healing of the lesion. This fact indeed is the basis of sanatorium treatment, which is so often successful.

So far as the tissues of the patient are concerned, there are also the important factors of immunity and allergy. It has now been abundantly proved that in most civilised communities infection by the tubercle bacillus is very common at some period of early life and that the healing of the resulting lesion, which is often of a slight character, confers a varying degree of immunity. In this country, for example, a positive tuberculin reaction is given by about 80 per cent. of the population. On the other hand, infection has also the effect of leading for a time to supersensitiveness or allergy (p. 194), and during this period the lesions tend to be intensified and to be of a caseating or exudative type. A healthy adult, previously infected and having a high degree of immunity, also has a certain degree of allergy. These conditions of acquired immunity and allergy thus play an important part, but it is often impossible to separate their effects from variations in natural resistance and susceptibility.

In accordance with what has been stated, pulmonary tuberculosis is of two main types, namely (*a*) that met with in natural conditions in the non-immunised child, and (*b*) as a re-infection in the partly immunised adult. Adult tuberculosis, however, is not synonymous with 're-infection tuberculosis' as a certain proportion of adults have escaped infection during the later years of life. It has been found, however, that in uncivilised people and in those coming into areas of infection for the first time, the disease runs a course somewhat similar to that occurring in the young child and often of rapid nature.

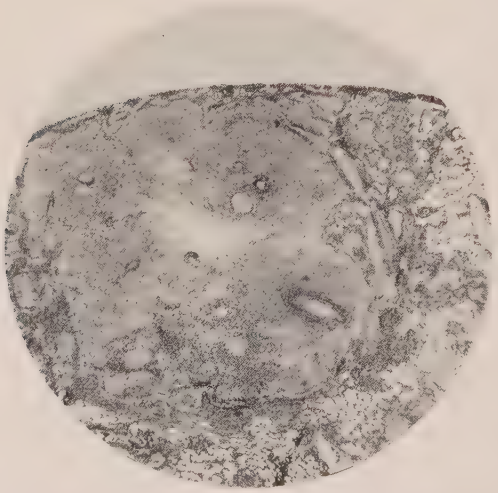

FIG. 270.—Primary Subpleural Tuberculous Focus in Child's Lung, showing the circumscribed character of the lesion and diffuse caseation. Some small tubercles are present on the periphery. (J. W. S. B.) × 5.

Pulmonary Tuberculosis in the Child. Here we have to do with implantation of the bacillus in what may be called a virgin soil. There is no acquired immunity or allergy, although there are variations in the natural resisting powers. The primary lesion is in the form of a localised area of caseating broncho-pneumonia, at the margin of which tubercle follicles are generally present (Fig. 270). It was first fully described by Ghon and for this reason is often spoken of as the 'Ghon lesion' (Fig. 271). It is usually sub-pleural in position, and may be met with on the surface of any part of the lungs, there being no tendency to affect specially the apex. When such a lesion has formed the subsequent results vary greatly. In the first place there may be extension by the lymphatics to the tracheo-bronchial glands which become greatly enlarged, diffusely caseous and often softened (Fig. 271). This is generally regarded as an allergic result. From the affected glands direct spread of the bacilli by the lymphatics to the large veins readily occurs and death often follows from miliary tuberculosis, sometimes attended by tuberculous meningitis. Again, there may be spread of the bacilli by the air passages and acute caseating broncho-pneumonia brings about the fatal result. These acute and serious results are the more apt to occur the younger the child is. On the other hand, a process of healing may occur round the primary lesion. It becomes encapsulated and the caseous material becomes calcified, and a similar process may occur in the corresponding caseous area in the related lymph gland (Fig. 272). It is noteworthy that in both situations calcification may be followed by ossification. Such calcified lesions can be readily found by X-ray examination and this method has been of great service in the study of the disease. The course of events after the primary infection of the lung depend not only on the resisting powers but also on the age of the child ; healing becoming more common as the years go on. It also varies in different localities. In Glasgow, according to Blacklock, in young children under three years the disease, once lesions have become manifest, is

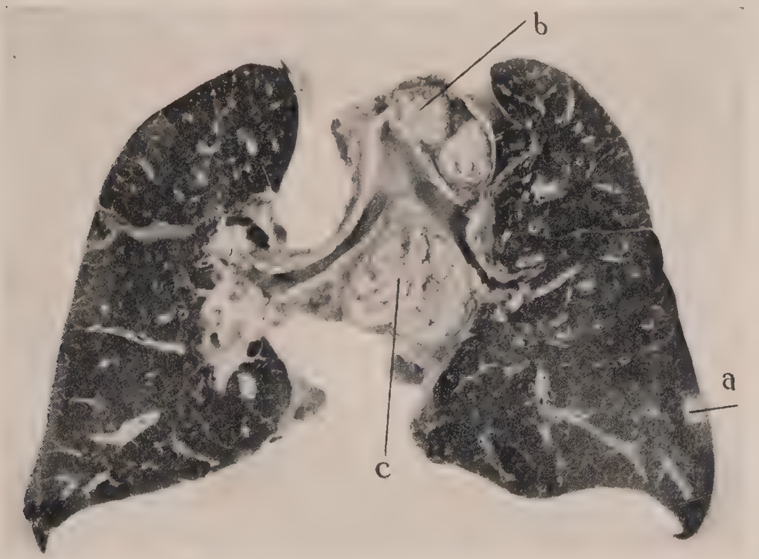

FIG. 271.—Lung of Child with (*a*) Primary Lesion in Right Lower Lobe, and (*b*) and (*c*) Enlarged Caseous Tracheo-bronchial Glands in relation to the Lesion. (J. W. S. B.)

usually fatal within a short time of onset, either from the extent of the pulmonary lesions or often from tuberculous meningitis. In a wide experience, he has only once seen a healed tuberculous lesion without evidence of further spread in a child under three years of age. At a later period of childhood primary pulmonary tuberculosis becomes less acute. From published accounts of the disease as met with in children, it would appear, however, that elsewhere, notably in Germany and America, healing of the primary lesion at an early age is much more frequent.

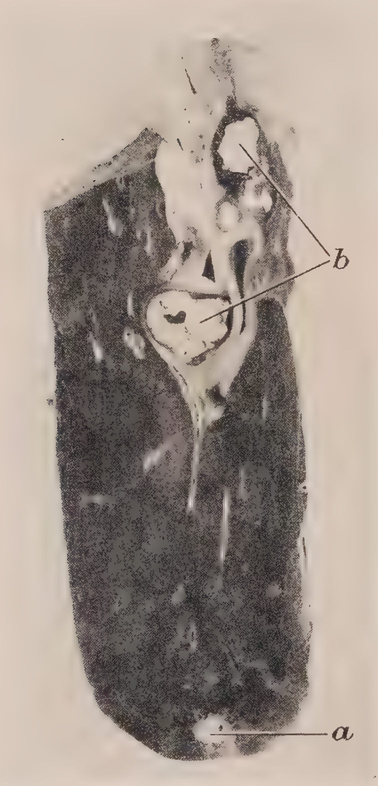

Fig. 272.—Old Ghon lesion in lung of child aged 7. (*a*) Calcified primary focus. (*b*) Calcified lymphatic glands. (J. W. S. B.).

It may be added that in nearly all cases of pulmonary tuberculosis in the human subject the bacillus is of the human type, though in Scotland about 4 per cent. are due to infection with the bovine type of bacillus.

Pulmonary Tuberculosis in the Adult. Here by far the commonest site of the primary lesion is the apex of the lung, or rather a short distance below the extreme apex; the right lung being the more frequently affected. This localisation has been ascribed to such factors as less movement just under the clavicle and less blood supply in that situation. But it must be admitted that the explanation of the apical infection is not clear. Such a lesion is now generally regarded as representing a re-infection. A state of venous congestion appears to have a defensive effect, and it is a striking fact that tuberculosis scarcely ever occurs in cases of mitral stenosis. The primary lesion in the apex is usually in connection with a minute bronchus, and thence the bacilli gain access to the lymphatics at an early period and spread along them, giving rise to lymphatic tubercles. Thereafter the lesion may undergo healing or may become the seat of a chronic ulcerative process with excavation, which leads to the characteristic apical phthisis of the adult. Thereafter other complications may follow.

Just as in the case of the pneumonias, so also with the varieties of tuberculous invasion the modes of spread rather than the histological features should be taken as the basis of classification. In accordance with this principle the various lesions will be considered as follows :—

(1) By the lymphatics, (*a*) *Chronic tubercle*, and (*b*) *Chronic tubercle with excavation*—'*Chronic phthisis.*'

(2) By the air passages, (*a*) *Tuberculous broncho-pneumonia*, and (*b*) *Caseating pneumonia with excavation*—'*Acute phthisis.*'

(3) By the blood stream, (*a*) *Acute miliary tuberculosis.* To this may be added (*b*) *Localised metastatic tubercle*—secondary to lesions elsewhere.

1. (*a*) *Chronic Lymphatic Tubercle.*

This is the lesion produced by a few bacilli settling in a portion of the framework of the lung and then slowly infecting adjacent parts. As has been said, it is the common initial lesion in adults, and apical in position as a rule. Tubercles usually occur in small groups in relation to the bronchi, and they have a greyish-white or yellowish colour, whilst at the periphery there is often an accumulation of carbon pigment (Fig. 273). They are comparatively firm to the touch, and there is often a considerable amount of fibrosis in the neighbourhood. A number of them may have become confluent and undergone caseation in the centre. Microscopic examination shows that the earliest change is the formation of chronic tubercle nodules, usually comprising several giant-cell systems (Fig. 274), and in the nodules the elastic tissue of the lung has disappeared. These nodules are chiefly in the peribronchial connective tissue, and there may be little or no reaction in the air vesicles around; or some consolidation may be present. Not infrequently a bronchus becomes invaded, its wall undergoing caseation and its lumen being blocked by caseous material. The lesion may, therefore, be regarded as a slowly spreading lymphatic tubercle with occasional implication of the lumen of the bronchioles and air vesicles.

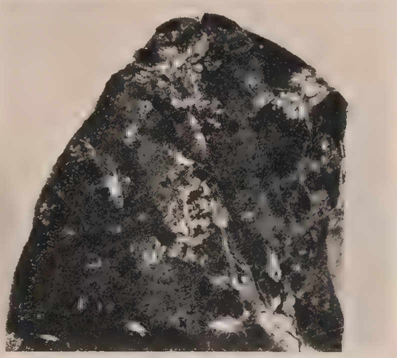

FIG. 273.—Chronic Lymphatic Tubercle of Apex of Lung.

Note the collections of grey tubercles without cavity formation. × $\frac{1}{5}$.

In connection with the earlier development of tuberculous lesions in the lungs, the occurrence of hæmoptysis is not uncommon; in fact, it is sometimes the earliest sign of the disease. The hæmorrhage is usually comparatively slight, though sometimes a small quantity of almost pure blood may be expectorated. It is apparently due to erosion of some of the smaller vessels, and is to be distinguished from the larger and more serious hæmorrhage from a cavity in the later stage of the disease, sometimes a result of rupture of a pulmonary aneurysm (p. 312). Another not infrequent early manifestation of pulmonary tubercle is serous effusion into a pleural sac (p. 425).

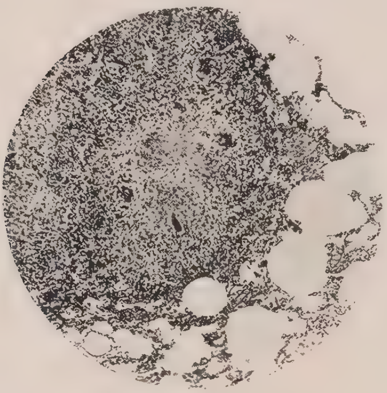

Fig. 274.—Chronic Pulmonary Tubercle, showing a Nodule composed of several Follicles, sharply demarcated from the surrounding tissue. × 45.

Whilst such changes may progress and lead to the next stage, viz. excavation, healing is the more usual result, as is shown by the frequent occurrence of scars, which vary according to the stage reached. There may be only a slight puckering at one or both apices with some adhesion of the pleura, or there may be an encapsulated caseous or calcareous patch, or, again, there may be a small cicatrised cavity. Such signs of old tuberculosis are very common in the lungs of patients who die from other causes. Apical tubercle is very rare before the age of ten years. Thereafter it gradually increases in frequency.

1. (*b*) *Chronic Tubercle with Excavation—'Chronic Phthisis.'*

As already said, this follows localised lymphatic tubercle, usually at the apex of one or both of the lungs, though sometimes in other parts. A small bronchus, surrounded by chronic tubercle nodules, may become invaded, and its lumen may be filled up with caseous material, which may then become discharged by the bronchus, a small cavity resulting. The same process going on in other parts, leads to formation of further cavities, and these afterwards become confluent. Cavity formation of this type is thus a slow ulceration of tissue already invaded by the tubercles. The bacilli, by their spread along the neighbouring lymphatics, give rise to further nodules which become involved in the ulcerative process, as may also small patches of caseating pneumonia. Such a process may advance very slowly, and there is then a great overgrowth of fibrous tissue, not only around the cavities but also in a diffusely spreading manner. In this way, a shrinking of the lung is of common occurrence, and bronchiectasis may be superadded. In fact, bronchiectatic cavities with red vascular lining are often found along with phthisical cavities whose walls are covered with caseous material. Ultimately, a cavity may reach a very large size, and may occupy a considerable portion of the upper lobe (Fig. 275). The walls of the chronic cavities are somewhat irregular and present raised bands, which represent obliterated blood vessels and other structures which have more resistance than the rest of the tissue. In very chronic cases their lining may be comparatively smooth, but there is usually adherent caseous material, or there may be grumous débris with sometimes an admixture of blood. The contents of the cavities have as a rule no putrid odour, and the organisms present along with the tubercle bacilli are chiefly of the pyogenic class; they aid the ulcerative process, while their toxins play a part in increasing the cachexia. Although the pulmonary vessels usually become obliterated before the ulcerative process reaches their interior, this may not happen. On the contrary, the wall of an artery may be weakened when the vessel still contains blood, and an aneurysm may result. A pulmonary aneurysm may be of the size of a pea or even of a cherry, and give rise to serious, sometimes fatal hæmorrhage by its rupture. It is a fact of importance that caseation in the related lymph glands is hardly ever present as a result of chronic fibro-caseous phthisis.

In some cases, the spread of the disease is so slow, and is accompanied by so much overgrowth of fibrous tissue, that the tuberculous nature of the lesion may largely be obscured. In such circumstances, the disease appears as a chronic fibrosis with much pigmentation, cavity formation of very chronic nature and also bronchiectasis. To such a condition the term *fibroid phthisis* has been applied.

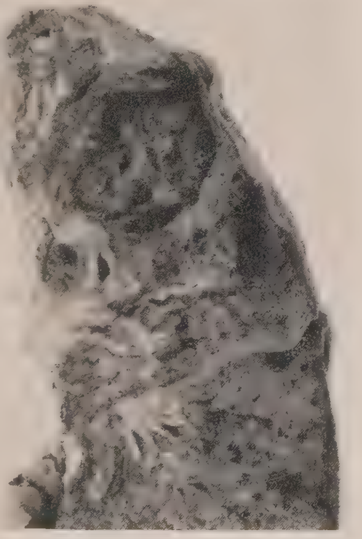

Fig. 275.—Chronic Pulmonary Phthisis.

A large irregular cavity occupies upper lobe and several smaller cavities are present in lower.

Although in ordinary chronic phthisis the spread of the disease is comparatively slow, there may be at any time a rapid diffusion of bacilli by the air passages, and thus a caseating pneumonia is superadded. It is not uncommon to find the latter in the lower parts of the lungs, whilst chronic cavity formation is present in the upper.

2. (*a*) *Tuberculous Broncho-pneumonia and* (*b*) *'Acute Phthisis.'*

These lesions are produced by dissemination of tubercle bacilli by means of the air passages. They are essentially similar in nature, the term acute phthisis being used when there is rapid caseation with cavity formation. The bacilli thus distributed may be derived from the breaking down of any local tuberculous lesion in the lung, or they may be set free by the ulceration of a caseous lymphatic gland into a bronchus. In the latter event, which is not uncommon in children, widespread infection by the air passages may occur within a short time and then the pulmonary disease has a relatively acute character from the outset.

In *tuberculous broncho-pneumonia* both lungs are usually affected, although one is often involved to a greater extent than the other. The lung tissue is studded with numerous small patches, which are arranged in groups or clusters round the terminal bronchi. These patches have a dull yellowish colour in the centre and are of comparatively firm consistence. Consolidated areas of considerable size may be formed by their confluence. If a small caseating area be examined microscopically, it is found usually to show in the centre a small bronchus with caseous wall, plugged with caseous material, and around this an area of dense caseous consolidation, both the walls of the air vesicles and their contents being merged in the caseous change. Further out, reactive change is seen within the air vesicles, in which are numerous rounded catarrhal cells, which often contain fatty globules. The tubercle bacilli, after reaching a minute bronchiole, may thus be said to produce broncho-pneumonic consolidation, which is followed by caseation.

In *acute phthisis* we have corresponding changes, but on a more extensive scale. Large areas of the lungs may contain caseous patches of considerable size, which are usually most abundant in the lower parts (Fig. 276). These are manifestly of pneumonic nature. In the central parts, the caseous material becomes softened, and cavities in various stages of formation may be present. The walls of these are very ragged and are lined by the remains of the air vesicles, the contents being caseous fragments and grumous material. Microscopic examination shows that the lesions are essentially of the same nature as in tuberculous broncho-pneumonia, but the affection is more severe and is often attended by a considerable amount of fibrinous exudation in addition to the catarrhal change (Fig. 277). The elastic tissue persists for a considerable time in the caseous alveolar walls, but afterwards becomes broken up in the process of cavity formation, and accordingly may be found in the sputum. In the formation of cavities in acute phthisis we may thus say that there are three stages, namely: (1) pneumonic consolidation; (2) diffuse caseation of the affected areas; and (3) the breaking down or excavation of the caseous material. Sometimes large areas of the lung may be implicated in the caseous process, the appearance thus resembling more a tuberculous lobar pneumonia. Occasionally, a localised portion of lung may undergo necrosis and form a soft slough, and when this involves the pleura, perforation and pneumothorax may result. These acute destructive changes are specially met with in those in whom no immunity is present as the result of a healed primary lesion. In such persons also lesions like those in primary tuberculosis in the child may occur.

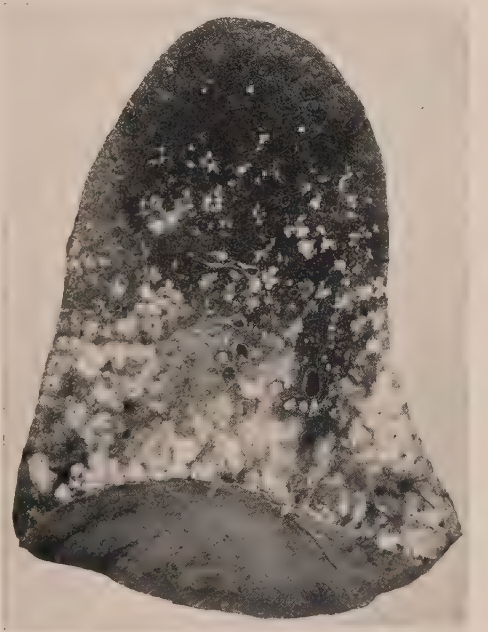

Fig. 276.—Acute Phthisis at comparatively early stage, showing numerous patches of Caseous Pneumonia in lower Lobe.

In phthisis, both acute and chronic, *tuberculous ulcers* are often set up in the intestines by bacilli in the sputum which has been swallowed. Tuberculosis of the larynx (p. 377), likewise produced by direct infection from the sputum, is a serious complication seen in a proportion of cases. *Amyloid* degeneration also may occur both in the intestines and other organs. In the former it gives rise to a profuse watery diarrhœa.

The chief *symptoms* in pulmonary tuberculosis, in addition to cough, hæmoptysis, etc., are advancing emaciation and asthenia with night sweats, a varying amount of secondary anæmia and pyrexia of irregular type. They are produced by the toxins of the tubercle bacillus aided by those of pyogenic and other organisms present in the lesions, and are most marked when caseation and excavation are advancing.

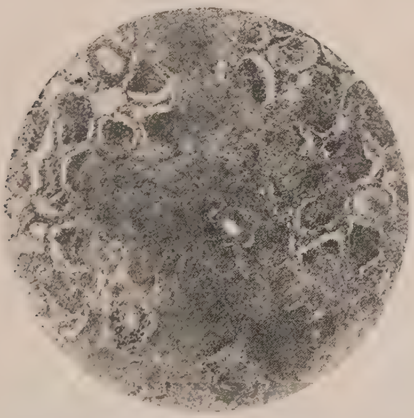

Fig. 277.—Section of Lung in Acute Phthisis, showing the characteristic Consolidation with diffuse Caseation of the Alveoli and their Contents. × 30.

3. (*a*) *Acute Miliary Tuberculosis.*

This is properly not a disease of the lungs, but a part of an acute general tuberculosis, and occurs when a considerable number of bacilli gain entrance to the blood stream. The modes by which this is brought about have already been considered (p. 98). It is to be noted that in miliary tuberculosis the nodules in the lungs are usually more numerous than in any other organ. Both lungs are usually equally involved and are beset with numerous small nodules of greyish appearance (Fig. 278), though sometimes they are larger and yellowish. They may be so small as to be just visible to the naked eye, or may be of the size of a pin-head. They are often more numerous and of rather larger size in the upper lobes than in the lower. Microscopically, the lesion is found to consist of a growth of minute tubercles in the framework of the lungs, especially in the peribronchial connective tissue and septa (Fig. 279). Each nodule starts from a capillary and the proliferation is primarily interstitial, but it is soon followed by catarrhal changes and consolidation in a ring of air vesicles. Coagulative necrosis then follows in the centre of the areas. There may be also formation of giant-cells, but in very acute cases this may be absent. Occasionally, just as in the spleen, the lesion is less acute, and the nodules are

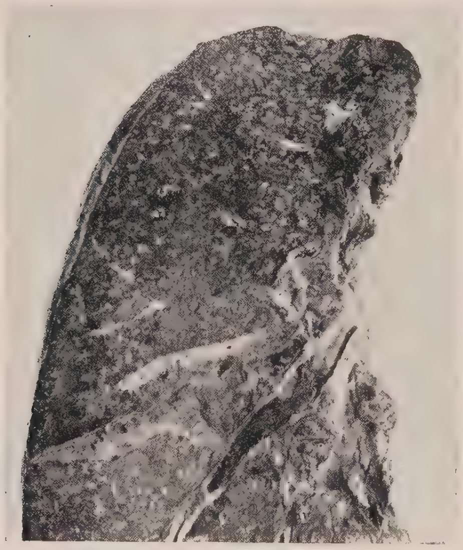

FIG. 278.—Acute Miliary Tuberculosis of Lung.

Note the small pale nodules scattered through its substance.

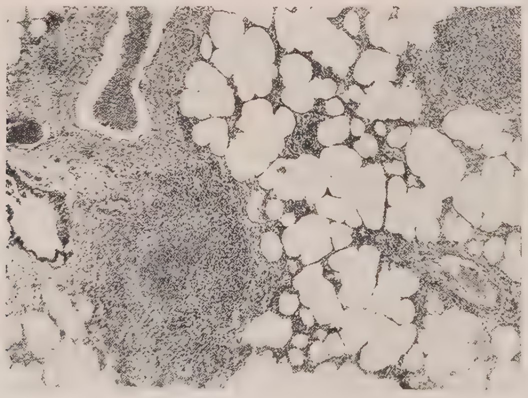

FIG. 279.—Section of Lung in acute Miliary Tuberculosis, showing two small well-circumscribed nodules. × 40.

less numerous, of larger size, and of a yellow caseous appearance. Such a condition will result when a smaller number of bacilli gain access to the blood stream. It may be added that in acute miliary tuberculosis, even although there is no breaking down of the lesions, tubercle bacilli may be found in the sputum, though in small numbers. Usually, however, none can be detected.

3. (*b*) *Localised Metastatic Tubercle.*

In tuberculous infections in various situations, not infrequently a few tubercle bacilli gain access to the blood stream and are carried to distant parts, where they give rise to localised tubercle. This is well seen, for example, in the case of the brain, bones, kidneys, and other organs. That secondary tubercle in the lung may be produced in this way cannot be doubted, and in view of the susceptibility of the pulmonary tissue, it is probably so produced fairly often. In such cases the effect will vary according to the conditions above described, being chiefly healing or extension.

THE PLEURÆ IN PULMONARY TUBERCULOSIS.

In tubercle of the lungs the pleural cavities are affected in various ways. At a very early stage of localised disease tubercles may form in the visceral pleura, and there may be an extensive effusion into the affected pleural sac. The fluid is usually of a clear character and the cells in it are scanty and mainly lymphocytes, whereas in the case of dropsical effusions met with in cardiac disease, there is usually a large proportion of desquamated endothelial cells. In many cases no tubercle bacilli can be found, and in such cases the presence of a fluid with the characters described is suggestive of the presence of a tuberculous lesion. Sometimes the exudate is sero-fibrinous and there may be some admixture of blood. The common result in chronic lesions is thickening and adhesion of the pleural layers in relation to the part, and in very chronic cases the thickening may reach a high degree. Owing to such adhesions perforation into the pleural sac is uncommon, even when many cavities are present; but in acute phthisis a necrotic patch in the lung may rapidly involve the pleura and cause pneumothorax, which is usually attended by inflammation and suppuration—pyo-pneumothorax. Apart from actual perforation, pyogenic organisms occasionally invade the pleural cavity and give rise to an empyema. Extension of tubercle to the parietal layer of the pleura is, on the whole, somewhat uncommon, but occasionally bacilli gain access to the cavity (as may occur from a tuberculous rib or vertebra), and there may be an eruption of tubercles on both layers; sometimes they are of considerable size. This is often attended by fibrinous exudation, and there may result great thickening of the pleural layers, whilst between them there is a collection of caseous material—that is, a chronic tuberculous pleurisy in the strict sense (Fig. 280). At a later period there may be calcification.

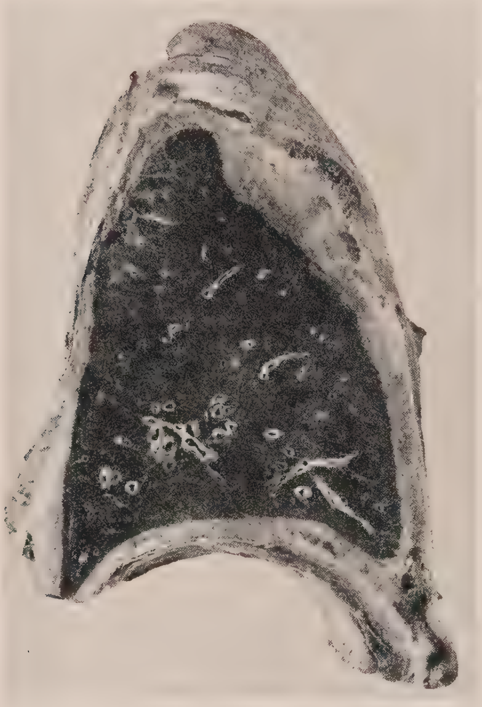

FIG. 280.—Chronic Tuberculous Pleurisy, showing enormous thickening of Pleural Layers with Caseous Material between. × $\frac{3}{5}$.

Syphilis

The syphilitic lesions of the lungs correspond in a general way with those in the liver, but are less frequent. In the *congenital* form, the chief lesion is an interstitial pneumonia of the cellular type. This occurs mainly in the peribronchial and perivascular regions, but it may extend diffusely and involve large areas, or practically the whole pulmonary tissue may be affected. In such conditions, the lungs have a pale appearance and tough consistence and contain comparatively little air; the somewhat unsuitable term of *white hepatisation* has been applied. The alveoli are of small size and many of them are lined by a cubical type of epithelium, whilst the small bronchi may undergo dilatation. Catarrhal changes are not infrequently superadded. The diffuse nature of these lesions is to be related to the large number of spirochætes which may be present in the pulmonary tissue. Gummata also may be present, and occasionally these reach a considerable size. In the *acquired* syphilis of the adult, gummata are met with but are rare. They show the usual characters and tend to undergo absorption so that cicatrices result. There is little doubt that, as in the liver, fibrous bands and diffuse fibrosis may be produced by syphilis, but it is often difficult to be certain that examples of such changes are of syphilitic nature. Syphilitic lesions in the adult are commoner in the lower lobes than elsewhere.

THE PLEURÆ

A number of affections of the pleuræ have been incidentally described, but others have to be added. Effusion of serous fluid into the pleural cavities, resulting in *hydrothorax*, is of common occurrence as a transudate in cardiac and renal cases; both pleural cavities are generally affected. It may also be produced by tumours or other lesions at the root of the lung, which interfere with the lymph flow. The presence of fibrous adhesions will prevent the accumulation, and when these are on one side, the corresponding lung is usually more œdematous than the other. *Hæmothorax*, or a collection of blood in a pleural cavity, is usually the result either of trauma, e.g. a perforating wound of the lung or severe fracture of ribs, or it is produced by rupture of an aneurysm. In some such cases the pleural cavity may be distended with blood and coagulum, and the lung is correspondingly compressed. The association of hæmorrhage with pleurisy will be referred to below.

Acute Pleurisy. The pleural cavity may be infected by organisms in various conditions. In one group of cases there is extension of organisms from some other inflammatory lesion, either in the lungs or in the neighbourhood; and in the other group the infection is by the blood stream. Pleurisy occurs whenever an inflammatory lesion of the lungs reaches the surface—for example, in acute lobar pneumonia, abscess, gangrene, septic infarction, etc. Sometimes it is the result of actual perforation, but more frequently the bacteria spread by the lymphatics. It may follow also as an extension from pericarditis, peritonitis, periostitis of ribs, and it may be set up by a hepatic or subphrenic abscess, either by perforation of the abscess or by lymphatic spread of organisms. Gastric ulcer, ulcerating carcinomata of œsophagus, of bronchi, etc., may likewise lead to infection of the pleura. Pleurisy may occur also secondarily to tumour growths in the pleuræ. Hæmatogenous pleurisy is met with in acute rheumatism, Bright's disease, septicæmias and infective fevers, scurvy, etc. The exudate in pleurisy varies greatly in character. It may be chiefly fibrinous—dry pleurisy; sero-fibrinous—pleurisy with effusion; semi-purulent, purulent, hæmorrhagic, or even of putrid or gangrenous type. The characters depend mainly on the organisms present. Thus pleurisy due to the organism of rheumatism or to the pneumococcus, is usually fibrinous or sero-fibrinous, though the exudate caused by the latter organism sometimes assumes a purulent character and empyema results. In streptococcus and staphylococcus infections, the exudate is usually purulent, whilst in the putrid type a great variety of organisms, both ærobic and anærobic, may be present. As in the case of the pericardium, a hæmorrhagic effusion is seen especially in scorbutic conditions and in invasion of the cavity by malignant growths.

The results vary according to the nature of the exudate. Serous and, to a certain extent, fibrinous exudate may undergo absorption, but in the case of the latter, a process of organisation is usually involved, and this will be in proportion to the amount and density of the fibrin. When suppuration has occurred the pus tends to increase in amount and sometimes forms an enormous accumulation, the lung becoming collapsed against the side of the vertebral column. A layer of granulation tissue then forms on the pleural surfaces, and this is followed by fibrous change in the layers. At the same time, fibrosis is apt to extend into the collapsed lung. When these changes have occurred the proper expansion of the lung is no longer possible, and hence it is of great importance that empyema should be treated before the changes involving permanent collapse have taken place. If an empyema is of comparatively small size, its contents may be absorbed or changed into a small collection of inspissated material ; great pleural thickening, sometimes followed by calcification, is apt to occur.

Chronic pleurisy, leading to pleural adhesions, may follow the forms of acute pleurisy mentioned above, or may be the result of chronic pulmonary lesions such as silicosis, tuberculosis, etc., as already described. We may say that from one cause or another the presence of some pleural adhesion is the rule after middle adult life.

Pneumothorax. This condition is produced by the entrance of air or gas into the pleural cavity and is usually the result of some breach of continuity of the lung substance. Thus it may occur secondarily to abscesses of the lung or gangrenous patches, and also to tuberculous lesions, especially when they are of the acute caseating variety. Pneumothorax is relatively uncommon in tuberculosis, nevertheless the latter is the most frequent cause of pneumothorax. In the conditions mentioned, the pleural cavity becomes infected with pyogenic and sometimes with putrefactive organisms, and pleurisy followed by suppuration is the common result, the condition being then called *pyo-pneumothorax*. The lung becomes, of course, greatly collapsed unless adhesions are present, and the changes described above in connection with empyema may follow. Occasionally, air gains entrance from the rupture of an emphysematous bulla, most frequently of the interstitial variety, as sometimes happens in whooping-cough. Pneumothorax may also be the result of injury, e.g. a punctured wound of the chest, or laceration of the lung from a fractured rib. In such conditions there may be no bacterial infection of the pleura, and if healing of the wound in the lung occurs, the air in the pleura rapidly becomes absorbed. Cases have been recorded in which the opening into the pleura has been of small size and has admitted the entrance but not the exit of air ; great distension of the pleural cavity with much displacement of the heart has resulted. Occasionally pneumothorax may occur suddenly in an apparently healthy individual. The air usually undergoes rapid absorption without any untoward effects. It is not possible to state definitely the cause of the pneumothorax in such cases, but it is probably the rupture of an emphysematous bulla. In rare cases gas gains access to a pleural cavity as a result of perforation from an ulcerative process in the stomach or intestines.

Tumours of the Lungs and Pleuræ

In the *lungs*, simple growths such as fibroma, leiomyoma and chondroma have been described, but they are all of very rare occurrence.

Carcinoma is by far the commonest primary tumour of the lungs. It usually takes origin from one of the main bronchi in the region of the root of the lung, though not infrequently from a bronchus in the substance. It may also possibly arise from the lung alveoli. Considerable attention has been given in late years to the incidence of cancer of the lung and most figures indicate a certain increase, though not so great as is often supposed. It is to be noted, however, that one type, the 'oat-cell carcinoma,' was formerly classified as a sarcoma. No distinctly pre-disposing or 'pre-cancerous' condition has been determined; no definite relation to chronic conditions such as tuberculosis, silicosis, etc., has been established. There is one exception to this general statement, namely, that there has been a high incidence of cancer amongst the workers in the Schneeberg cobalt mines in Saxony. It is doubtful whether the cobalt itself is the carcinogenic agent and it is thought likely that radio-active substances are concerned. It has been shown experimentally that exposure to certain dusts, especially in combination with tar, raises the incidence of adenomatous growths in the lungs of rabbits, which sometimes become carcinomata. (Campbell and others.)

Lung carcinomata as a group present a variety of histological characters. The commonest type is the 'oat-cell carcinoma,' the nature of which has recently been established by the observations of Barnard and others. In this group the cells are round, oval or spindle-shaped, with little cytoplasm, and form masses filling alveolar spaces. Here and there are often to be found transitions from such cells to those of a columnar type and occasionally the latter are readily found (Figs. 281, 282). The 'oat-cells' resemble somewhat those in the deepest layer of the epithelium of the large bronchi. The tumours of this class are often somewhat soft and of massive character; they early give rise to metastases. They are said to occur at a rather earlier age than the other types. Adeno-carcinomata, though less frequent, are still fairly common; they also may form large masses or give rise to denser infiltrating growths. The cells are of the tall columnar variety, but transitions to aberrant forms may be present; occasionally a papilliform type of growth is present. Squamous epithelioma is by no means rare. It is supposed to arise from the epithelium of bronchiectatic cavities which has undergone metaplasia, but as a rule the origin cannot be traced. Another type of carcinoma is one in which the lung becomes consolidated without its structural outlines being destroyed, the appearances resembling those of pneumonia. The cut surface presents a somewhat mucoid character. In cases of this type the growth is really within the alveoli, which may be lined at places by short columnar or cubical cells. It seems possible that this growth may arise from the alveolar epithelium, but this cannot be definitely stated.

All forms of carcinoma infiltrate widely by the lymphatics and give rise to secondary growths in the lung substance, glandular enlargements, etc. Implication of the pleura is common ; it may be covered with a thick layer of growth or be the seat of nodules. Pleurisy with effusion may result and the effusion has usually a hæmorrhagic character. Metastases in other organs are common and often occur early. The liver, adrenals, brain and kidney are common sites. As carcinoma usually originates at the root of the lung, it produces important results by obstructing the bronchi (Fig. 283), thus leading to bronchial dilatation, collapse of the lung, etc. A common result is that accumulation of secretion takes place beyond the obstruction, and in this bacteria grow readily and give rise to pus formation. Infection may spread back to the lung substance and the formation of abscesses in it may follow.

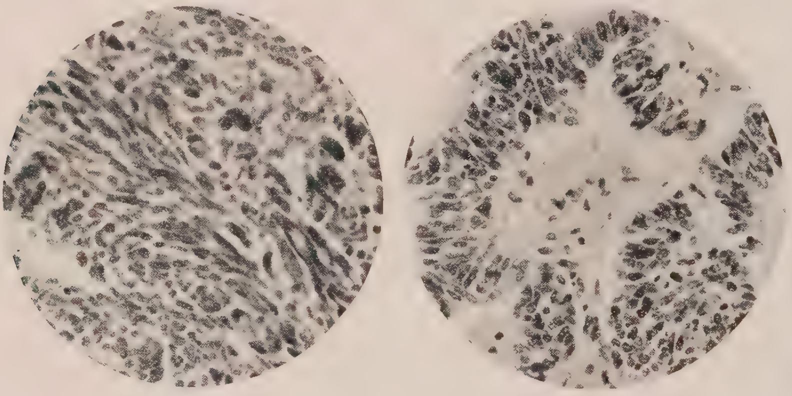

Fig. 281. Fig. 282.

Figs. 281 and 282.—Section of Oat-cell Carcinoma of Lung. Fig. 281 shows spindle-shaped and oval cells. In Fig. 282 transitions to cells of columnar epithelial type are seen. (Dr. J. F. Heggie.) × 220.

Primary *sarcoma* and *endothelioma* are occasionally met with in the lungs, but are rare. Any form of malignant growth in the lungs may give rise to hæmoptysis, and this is sometimes an early symptom.

Secondary tumours in the lung are fairly frequent in the case of *sarcomata* of all kinds. The metastases occur chiefly by the blood stream, and the tumours in the lung are usually multiple. The spread of *carcinoma* also to the lungs may take place by the blood stream, but we believe that the lungs more frequently become involved by means of the lymphatics. For example, in cases of mammary carcinoma, the cells may spread to the pleural lymphatics and thence to the lungs, whilst in cases of abdominal carcinoma there may be a spread to the bronchial glands, and from them extension into the lungs may follow. When the lymphatics of the lungs become involved, the growth may be of very diffuse character and produce only very minute nodules. The pleural lymphatics may, for example, appear as whitish threads outlining the lobules, and we have seen cases where the lungs contained very numerous nodules, no larger than tubercles and in some instances hardly palpable. On the other hand, of course, larger masses may form. *Lympho-sarcoma*, involving the bronchial lymph glands, either primarily or secondarily, has a great tendency to extend along the peribronchial lymphatics, forming sometimes an encasing sheath to the bronchi and also irregular masses of growth (Fig. 284). It is, however, relatively rare: many of the cases formerly described were really cases of oat-cell carcinoma. The appearance and distribution accordingly resemble those of cancer, but the tissue tends to be somewhat more cellular with an even greater tendency to necrosis than in the latter condition.

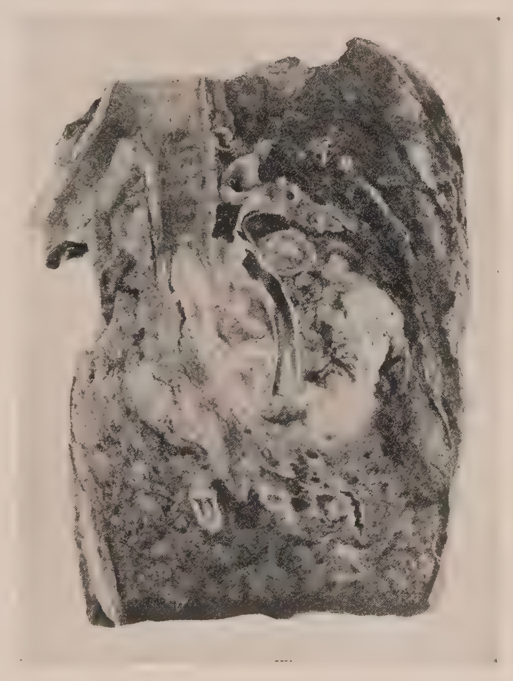

FIG. 283.—Cancer at Root of Lung causing Obstruction of Bronchus.

In the *pleura*, simple growths, e.g. fibroma, angioma, and subserous lipoma have been met with, but their occurrence is quite exceptional. *Primary* malignant tumours are more common though still rare, and of these the most characteristic is the so-called endothelioma of the pleura. The growth tends to involve the whole surface, and both pleural layers may be fused together and changed into a thick mass of growth encasing the lung. In other cases there are nodules in both layers and inflammatory exudate between; extension may take place to the pericardium and also along the lymphatics into the interior of the lung. Such growths have usually an alveolar structure like a cancer, but the cells vary in character; sometimes they are flattened and arranged in concentric fashion, as in an epithelioma, but without cell-nests; sometimes they are more rounded in form. Their origin is usually ascribed to the covering endothelium of the pleura. Some malignant growths of the pleura have more the features of a diffusely growing sarcoma. The occurrence of *secondary* growths, both of sarcoma and carcinoma, is not uncommon, as will be readily understood. As in the case of the pericardium, malignant growth is often attended by fibrinous or hæmorrhagic exudate.

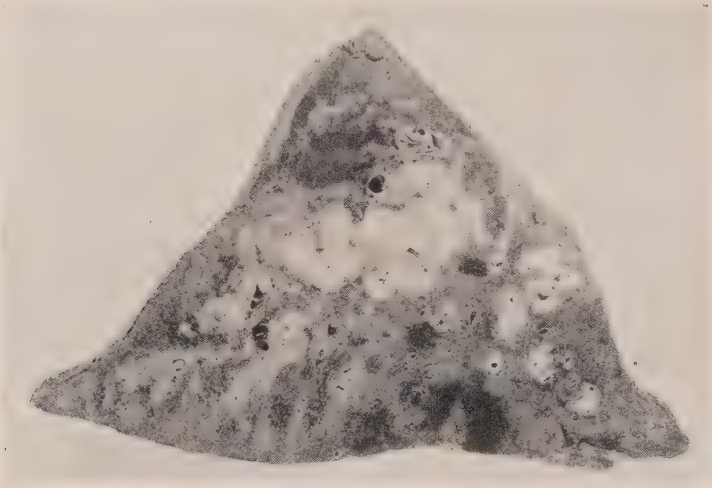

Fig. 284.—Section of Lung, showing Invasion by Lympho-sarcoma.
The whitish areas of tumour growth are enclosing the bronchi and obliterating their lumen.

CHAPTER XI

HÆMOPOIETIC SYSTEM

THE BLOOD [1]

Introductory. The term 'diseases of the blood' is often used and is convenient; but from the standpoint of cellular pathology it is not quite correct, as the blood is not a tissue or organ but the product of various tissues or organs. This is true, not only of the plasma but also of the cellular elements; they are supplied to the blood but do not normally multiply in it. The so-called diseases of the blood are mainly diseases of the hæmopoietic tissues, though various other organs may be concerned in the production of its pathological states. It is important to recognise that the body possesses a remarkable regulating mechanism whereby the state of the blood is kept wonderfully constant. Blood volume, specific gravity, chemical content, number of red corpuscles and leucocytes, varieties of leucocytes, etc., each has its normal average, and if in conditions of health any one of these is artificially altered, a return to normal occurs within a comparatively short time. The morbid changes in the blood thus come to be of great importance, and not infrequently are the means of supplying a diagnosis of the condition present. These changes may affect either the formed elements or the plasma; and though microscopic examination is the method most frequently employed, the importance of chemical examination is becoming more and more recognised. Thus clinical methods for estimating the amount of urea, glucose, bilirubin, cholesterol, etc., are now generally used and are of great service.

We shall consider first the changes in the corpuscular elements, while the main chemical changes, including variations in the amounts of the substances mentioned above, will be dealt with in connection with the diseases of the various organs concerned in their production.

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[1] For details the student is referred to special works, such as *The Blood*, by G. Lovell Gulland and A. Goodall, 3rd edition, Edinburgh, 1925; *Traité technique d'Hématologie*, by J. Jolly, Paris, 1923; *Recent Advances in Hœmatology*, by A. Piney, London, 4th edition, 1939; *Blutkrankheiten und Blutdiagnostik*, 5th edition, by O. Naegeli, Berlin, 1931; *Disorders of the Blood*, by L. E. H. Whitby and C. J. C. Britton, 3rd edition, London, 1939; *Handbook of Hœmatology* (4 vols.), edit. by H. Downey, London, 1938.

One must recognise that the marrow is the all-important tissue in supplying the formed elements of the blood ; it is the source of the erythrocytes, granular leucocytes, and platelets. All these are in a sense end-products ; there is no multiplication of them in the blood stream, though, as described below, both erythrocytes and leucocytes undergo a process of ripening after having entered the blood. The term *erythron* was proposed by Boycott to indicate the erythroblasts and their products, the erythrocytes, and is appropriate. In a corresponding way, *leucon* might be used to signify the myelocytes and the leucocytes formed from them.

THE RED CORPUSCLES

(A) **Variations in Number.** The number of red corpuscles per c.mm. varies greatly and its estimation is an important clinical method. Whilst variation is usually in the direction of decrease—*oligocythæmia*—there are certain conditions where an increase occurs —*polycythæmia.* In the first place, the number may be increased simply by the withdrawal of fluid from the blood, e.g. by profuse perspiration or by diarrhœa. The most striking example of this is met with in Asiatic cholera. In cases of this kind there is, of course, no alteration in the total number of corpuscles, simply an increased concentration of corpuscles ; the number soon returns to normal by addition of fluid when recovery takes place. When a person resides in a high altitude, an increase in the number of corpuscles per c.mm. is observed. This may amount to about 2,000,000 per c.mm. at an altitude of about 14,000 feet, and the increase of the total amount of the hæmoglobin in the blood is practically proportionate, the colour index being unaltered. The members of the expedition to the Andes in 1921–2 found that in individuals after arriving, there occurred an increase in the number of the young corpuscles or *reticulocytes* (p. 437), but that in individuals who had lived for a time at a high altitude the proportion of reticulated to ordinary corpuscles was practically normal. In the former there was evidently an increased proliferation of the erythroblasts in the marrow going on ; whilst in the latter a hypertrophy of the marrow had occurred and the erythroblasts were producing young corpuscles at the normal rate, so that the proportion of the young to the adult cells had reached the normal figure. The condition is to be regarded as a compensatory one, brought about by the diminished oxygen tension in the atmosphere. An interesting fact is that a converse effect also holds good. Living in an atmosphere with an excess of oxygen causes a reduced number of reticulocytes in the blood, and transfusion of blood has a similar result (Boycott and Oakley). This effect probably represents a diminished production of eruthrocytes, but the possibility that it may be due to raising the level of maturity at which they are discharged into the circulation cannot be excluded.

In cases of congenital heart disease there is often an increase in the number of corpuscles, the number per c.mm. sometimes reaching 7,000,000 or even more. A similar change, though usually less in degree, may be met with in cases of chronic venous congestion in adults, e.g. in mitral stenosis. It is to be regarded as of compensatory nature. In these conditions there is, of course, no deficiency of the oxygen-carrying power of the blood, but either a diminished amount of blood passes through the lungs in unit of time, or in some congenital cases venous blood passes directly into the left ventricle through a deficiency in the septum. Hence in both conditions there is an advantage in having a greater concentration of hæmoglobin in the blood.

In primary polycythæmia with splenomegaly (p. 483) the number of red corpuscles may occasionally rise above 8,000,000 per c.mm., and it has been found that there is also increase in the blood volume (Boycott) ; thus true plethora as well as polycythæmia is present. In this case there is no evidence that the increase is of compensatory nature.

Decrease in the number of red corpuscles per c.mm.—*oligocythæmia*—is very common, and may be produced in various ways, as will be described later. The term ' anæmia ' is sometimes used as synonymous with oligocythæmia, but it is better to use it as including all conditions where there is a diminution in the percentage of hæmoglobin ; the two conditions are usually associated, but there may be considerable anæmia with little or even no diminution in the number of red corpuscles. The most severe examples of oligocythæmia are met with in the so-called primary anæmias ; for example, in pernicious anæmia the number of red cells may fall to 500,000 per c.mm., or even to a lower level. It may be added here that in all cases the percentage of young cells or reticulocytes in the blood gives a valuable indication as to the amount of blood formation which is going on.

(B) **Changes in Size and Shape.** Oligocythæmia is frequently associated with variations in the size of the corpuscles—*anisocytosis*—and irregularities in form—*poikilocytosis*. Corpuscles larger than the normal, or *megalocytes*, are specially numerous in pernicious anæmia and some related anæmias ; the circular forms may measure 10–12 μ in diameter, whereas the oval forms may be even larger (p. 453). Although undersized forms also are present, the *average size* of the corpuscles is usually greater than the normal, and the anæmia is thus spoken of as *megalocytic*. The typical megalocytes in pernicious anæmia appear well coloured, owing to the amount of hæmoglobin they contain ; but over-sized corpuscles, usually pale and somewhat swollen in appearance, may be met with in other types of anæmia. Corpuscles smaller than the normal, or *microcytes*, occur in all forms of anæmia, but they preponderate in certain types so that the average size of the corpuscles is diminished ; the anæmia is then called *microcytic*. Microcytes may measure 4 μ in diameter or even less ; the smallest forms are probably produced by a splitting off from the larger corpuscles.

Price-Jones has introduced the method of plotting curves which give a graphic representation of the size of 500 red corpuscles in any specimen of blood. The base line gives the size of the corpuscles in microns and the ordinate represents the number of red cells amongst the 500 giving any particular size. The normal curve resulting is an almost symmetrical pointed curve with its apex corresponding approximately to the average mean diameter of the corpuscles; the base of the curve shows the variations in size met with. With such a curve as a standard, the condition of any abnormal blood can be compared. Thus in pernicious anæmia there is a shift of the curve to the right, owing to the increase in the average size of the corpuscles, while the base of the curve is increased owing to greater variations in their size. In secondary anæmias, on the other hand, there is a shift to the left.

Corpuscles of irregular shape, known as *poikilocytes*, may be met with in any form of marked anæmia (Figs. 294, 295). Their presence in itself has no diagnostic importance, nor is their number in proportion to the severity of the anæmia. They are usually a striking feature in pernicious anæmia, they occur also in other anæmias, occasionally being numerous; we have seen them in enormous numbers in severe anæmia following repeated hæmorrhages.

Another pathological variation is that the erythrocytes may be thicker than normal while their diameter is less than normal. They thus tend towards a globular shape and the term *spherocytosis* is applied. It is a characteristic feature of acholuric jaundice (p. 465). Still another abnormality is the sickle-form assumed by the corpuscles in sickle-cell anæmia (p. 467.)

The real average size or mean corpuscle volume can readily be calculated as follows: The corpuscular volume of a sample of blood is ascertained as a percentage by centrifuging in a hæmatocrit; the normal is about 45. The mean corpuscular volume is then got by dividing the volume of packed corpuscles in a c.mm. by the number of red corpuscles per c.mm; the normal = 78 — 94 cμ.

(C) **Variations in Hæmoglobin.** These are, for clinical purposes, usually expressed as percentages of the normal for a given amount of blood; the figures thus indicate the concentration of hæmoglobin in the blood, and, in order to estimate the total hæmoglobin, the blood volume must be known in addition. The relative amount of hæmoglobin per corpuscle, or *colour index*, is of importance, and is obtained by dividing the percentage of hæmoglobin, as estimated by the hæmoglobinometer, by the percentage of corpuscles per c.mm., in relation to the normal. Thus, for example, if the hæmoglobin is 45 per cent. and the number of red corpuscles is 3,150,000 per c.mm. (63 per cent. of the normal), the colour index will be 45/63, that is, approximately 0·7. The colour index varies in different types of anæmia and the terms *hyperchromic* and *hypochromic* are applied according as it is raised or lowered. Thus, in megalocytic anæmias, e.g. pernicious anæmia the colour index is usually above 1, often 1·2 or even more. The other extreme is met with in the primary hypochromic anæmias, where the colour index may be greatly reduced, being sometimes 0·5 or even less. It should be noted that an increased colour index is always due to increased average size or rather volume of corpuscles. There is no evidence that the *concentration* of hæmoglobin in the corpuscles ever rises above the normal. A lowered colour index may be due to diminished average size of corpuscles or to diminished concentration of hæmoglobin, or to both combined.

One may add that the eosinophile staining of the red corpuscles depends on the hæmoglobin and a rough estimate of its amount may be got from the appearance of a stained film. When the hæmoglobin is markedly deficient in amount, the red staining is present only at the periphery, giving the so-called 'ring staining.'

(D) **Polychromasia and Reticulocytes.** If a film of blood from a normal individual be stained with a combination of a basic and acid dye such as Jenner's or Leishman's stain, practically all the erythrocytes are stained a uniform red colour, that is are purely eosinophilic. In certain conditions, however, a certain proportion of the erythrocytes have a bluish violet tint of varying depth; in other words they show a slight degree of basophilia added to the eosinophilia. To this altered staining reaction the term *polychromasia* or *polychromatophilia* is given, and the importance is that the erythrocytes showing it are young corpuscles, which have recently lost their nuclei. Such corpuscles thus become numerous when there is increased formation in the bone-marrow, for example, after hæmorrhage. As they ripen in the circulation the polychromasia gradually disappears and the ordinary reaction is given. The young erythrocytes tend on the whole to be slightly larger than those thoroughly mature. They may show also a certain amount of adhesiveness.

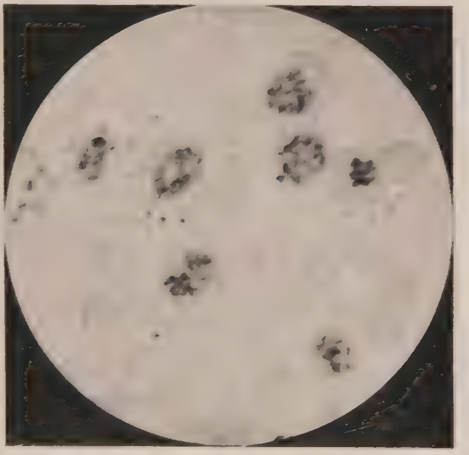

FIG. 285.—Rabbit's Blood in Hæmolytic Anæmia, showing the characters of Reticulocytes which in this case are also Megalocytes; Platelets also are present. × 1000.

Another means of recognising young erythrocytes is afforded by methods of supra-vital staining with suitable dyes, cresyl blue being most frequently used. The action of such dyes is to produce a sort of coagulation or condensation into threads of the basophile substance in the young erythrocytes, which then show a sharply stained skein-like structure or reticulum in their interior (Fig. 285). Such corpuscles are called *reticulocytes*. The reticulum becomes less and less as the corpuscles ripen and ultimately disappears. Polychromatophilic corpuscles and reticulocytes alike represent young erythrocytes and their number in the circulating blood affords a valuable means of estimating the amount of blood formation that is going on. Enumeration of such corpuscles as reticulocytes is the easier and more exact method, since a very small reticulum may be insufficient to alter the staining of the erythrocyte by one of the ordinary methods. In normal blood reticulocytes are present in a proportion of about 1 per cent.

A very suitable method for applying such a stain as cresyl blue is to make a film on a clean slide with an alcoholic solution of the dye and allow it to dry; a drop of blood is then placed on the dry film, a cover-glass is placed over it and examination made in the usual way. The reticulum becomes formed and takes up the dye, becoming coloured intensely. Another method is to mix the blood with a suitable concentration of the dye in citrated saline.

Another alteration in the red corpuscles is known as *punctate basophilia* (Fig. 286). In this condition some red corpuscles are studded with minute granules which give a marked basophile reaction like chromatin, though they do not necessarily represent this substance. Punctate basophilia occurs especially in anæmias produced by toxic substances. It is often a well-marked feature in chronic lead-poisoning, and it can be produced in animals by administering small doses of lead for a period of time. It is interesting to note that it may occur in lead-poisoning when there is little anæmia, and its presence is sometimes of value in diagnosis. It is met with in pernicious anæmia and may be produced experimentally by various hæmolytic poisons. Punctate basophilia may be associated with polychromatophilia in the same corpuscle, and the appearance is as if the one condition sometimes passes into the other, the diffuse basophilia becoming less marked as the granules become more distinct. It would seem that punctate basophilia is an abnormality produced in most cases by toxic action on the erythroblasts, as these show the condition as well as the erythrocytes. It probably represents a granular change in the basophile substance of the young erythrocytes—the substance which forms reticulum when condensed.

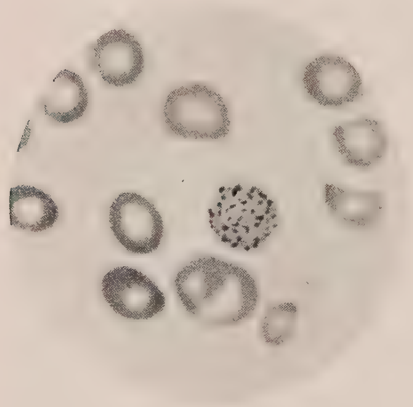

Fig. 286.—Film of Blood from a case of Pernicious Anæmia; Punctate Basophilia is present in a Red Corpuscle. × 1000.

Cabot's 'Ring-bodies.' Single or multiple coarse basophile granules, apparently nuclear remains, are occasionally met with in the red corpuscles in anæmic conditions, but special interest is attached to the ring-bodies described by Cabot on account of their characteristic appearance. They are outlined by continuous threads which usually form rings, but also loops, figures of eight and rosettes; occasionally granules are present along the course of the threads. Illustrative examples are shown in Figs. 287 and 288. The corpuscles in which they lie are usually polychromatic and they can be conveniently demonstrated by prolonged treatment with Giemsa's stain. They are met with especially in pernicious anæmia but occur also in other forms of anæmia—leukemia and lead poisoning. Ring-bodies are usually supposed to be comparatively rare, but McCluskie was able to demonstrate them in eight successive cases of pernicious anæmia. Cabot supposed that they represent nuclear remains and this view has been generally accepted. It may be mentioned that they occasionally occur outside the red corpuscles.

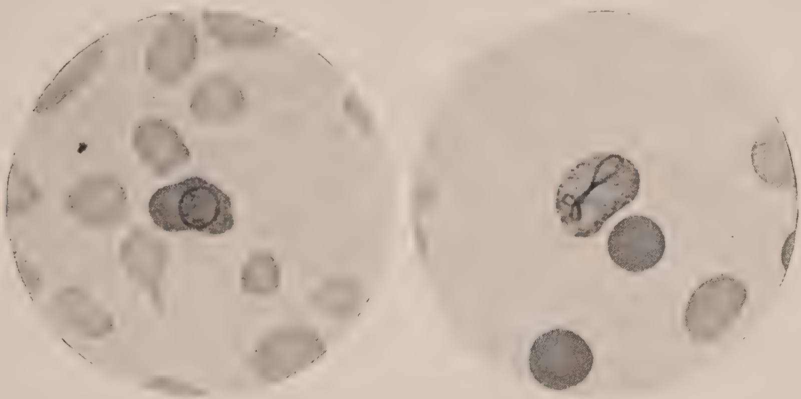
FIG. 287. FIG. 288.

FIGS. 287 and 288.—Cabot's ring-bodies within Red Corpuscles in Pernicious Anæmia. (Dr. J. A. W. McCluskie.) × 1000.

(E) **Presence of Erythroblasts.** Nucleated red corpuscles, which normally are present in the adult only in the marrow, appear in the circulating blood in a variety of conditions. In accordance with Ehrlich's description they are usually regarded as being of two main types, viz. *normoblasts* and *megaloblasts.* In the fœtus the first nucleated red cells to appear are megaloblasts, which produce megalocytes. Later, normoblastic hæmopoiesis appears, and has replaced the megaloblastic type by the time of birth. It has been suggested by some that this change in the character of blood formation may depend on the growth of stomach or of liver.

Normoblasts are of about the size of an ordinary red corpuscle or a little larger, and have a single spherical nucleus which is very rich in chromatin and thus stains very deeply. The nucleus may show a coarse reticulum of deeply staining chromatin, or it may appear very dense and practically homogeneous, the latter being the common appearance of the smaller nuclei, which are met with in the older erythroblasts (Fig. 292). The nucleus may be fragmented into two or more rounded pyknotic portions. It may be said that normoblasts may occur in various types of anæmia. Occasionally a large number somewhat suddenly appear in the circulation; such an occurrence is known as a 'blood-crisis,' and it usually indicates a period of specially active regeneration, though it may sometimes have some other significance (Fig. 300). Normoblasts are sometimes very numerous in the myeloid form of leukæmia.

The *megaloblasts*, as their name indicates, are of larger size; the nucleus is fairly large and usually stains less deeply than the nucleus of a normoblast, and shows a somewhat granular or reticular structure (Fig. 295); it may be also fragmented or pyknotic. The protoplasm of megaloblasts often gives a polychromatophilic reaction of varying depth, and may show punctate basophilia. Mitotic figures may be observed in the erythroblasts in the blood, especially in megaloblasts, but their occurrence is rare. Pernicious anæmia is a disease in which the presence of megaloblasts is an important feature, and at least a few are to be found as a rule; they are usually associated with normoblasts. They are met with similarly in the other types of megalocytic anæmia referred to later (p. 460). It is to be noted that in anæmias in children, megaloblasts appear much more frequently in the circulating blood than they do in adults. Apart from these conditions, the occurrence of megaloblasts is relatively rare.

Whilst, as has been said, the presence of erythroblasts in the circulation usually indicates special regenerative activity on the part of the bone-marrow, it has not always this significance. In myeloid leukæmia, for example, these cells are often present in the blood in large numbers, and they would appear to be swept into the circulation along with the other cells from the marrow (p. 477). When the bones are extensively invaded by malignant growth, erythroblasts may be present in the blood, and this may be due to a stimulating effect on the marrow—some parts are destroyed, the others become more active—or, on the other hand, it may simply represent the result of disturbance of the marrow by the new growth. Again, in some very severe infections, such as hæmorrhagic smallpox, erythroblasts may appear in the blood, often accompanied by a few myelocytes; there is here no question of special regenerative activity, and probably both types of cells enter the blood as a result of damage done by toxic action to the delicate structure of the marrow. The appearance of small numbers of erythroblasts in the blood shortly before death, is probably to be interpreted in a similar manner.

There has been, and still is, confusion in the use of the term megaloblast. It is best to restrict the term to a large hæmoglobin-containing cell which has as its natural product a megalocyte. This was the sense in which Ehrlich first applied the term and he recognised that such cells occur in pernicious anæmia and also in normal blood formation in the fœtus. According to this use of the term, megaloblasts do not occur in normal hæmopoiesis *in the adult.* The larger cells which are the precursors of normoblasts, should be called primitive erythroblasts, basophile or polychromic as the case may be. Some recent writers have restricted the term megaloblasts to the cells in pernicious anæmia, holding that they have special distinguishing features. If this is the case they should be distinguished by calling them pathological or P-A megaloblasts, or by some other name. It should be noted that megaloblastic hæmopoiesis may be induced in lower animals by toxic agencies, for example, by a hæmolytic serum in the rabbit. (Note the megalocytes induced in this way in Fig. 285.)

Variations in the Resistance of the Red Corpuscles. It is well known that when red corpuscles are placed in a hypotonic salt solution the hæmoglobin dissolves out. The highest concentration at which this occurs may be observed and taken as indicating the resistance (' minimum resistance ') of the corpuscles. In order to estimate the resistance, the red corpuscles are separated from the serum by centrifuging and washing in saline solution, and are then distributed in tubes containing sodium chloride solution in graduated concentrations. The tubes are centrifuged after a period of about fifteen minutes, or natural sedimentation is allowed to occur, and then the tube in which there is the first trace of lysis, as shown by slight colouration of the saline, can be noted. With a normal blood, the first trace of lysis is usually seen in a concentration of 0·42–0·46 per cent. of sodium chloride ; initial lysis occurring below 0·4 or above 0·5 per cent. may be taken as indicating an abnormal condition, and is spoken of as increased or as diminished resistance respectively. The latter condition is known also as *increased fragility*. The best known example of diminished resistance of the red corpuscles is met with in the familial type of acholuric jaundice with splenic enlargement, where the minimum resistance may be at 0·6 per cent. or even higher. It is to be noted that in such cases the fragility has been found to persist unchanged after removal of the spleen, even although the anæmia largely disappears. The resistance may be lowered somewhat in other hæmolytic anæmias and cachectic conditions, but the results obtained are not constant. A marked increase of the resistance has been observed in the anæmia experimentally produced by phenylhydrazine. In obstructive jaundice the resistance of the red corpuscles is usually distinctly increased.

Sedimentation Rate. This is a subject which has been extensively studied in recent years. The general principle is to add an anti-coagulant to a certain amount of blood, place the mixture in an upright calibrated tube and observe the rate of sedimentation of the red corpuscles, as indicated by the amount of clear fluid after a given period of time. This can be compared with the normal rate. Variations in disease are chiefly in the direct of increased rapidity of sedimentation and these generally indicate increased metabolism or breakdown of tissue as produced by toxic and infective conditions. The test has no specific value but has been found useful as an aid to recognition of organic disease, and notably as a prognostic aid in a particular condition, notably in tubercle. Approximation of the rate to normal is taken as a favourable sign.

THE LEUCOCYTES

Introductory. In connection with the part played by leucocytes in conditions of disease, the distinction between the myeloid and lymphoid tissues is of prime importance. The two tissues differ in their place and time of development in the fœtus, and also as regards the cells derived from them both in fœtal and in adult life ; whilst in disease they react independently, are the seat of different lesions, and there is no evidence of transition between the cells of the one series and those of the other. Myeloid tissue, restricted to the red bone-marrow in the adult, is related to the blood and produces through its myelocytes all the granular leucocytes ; and with the myelocytes, areas of proliferating erythroblasts are usually associated.

Thus it follows that most of the morphological changes in the blood are either the result of reaction on the part of the cells of the myeloid tissue or the effects of diseases of it. Response to the requirements of the body or to stimulation has now been pretty fully studied, alike in the case of the red corpuscles, the neutrophile and eosinophile leucocytes ; and the mode of reaction is fairly well understood (p. 77). Possibly, non-granular cells of the marrow react in a similar way. The lymphoid tissue, on the other hand, is essentially related to the lymph stream, and the cells produced by it are all of the non-granular type. Its diseases are of a different kind, and it is remarkable how widespread its lesions may sometimes be without accompanying change in the blood. There is, in fact, in lymphoid tissue no structural arrangement such as exists in the marrow by which its cells may pass easily into the blood in response to chemotactic influences.

There has been much discussion as to the origin of the mononuclear leucocytes or monocytes but the general tendency now is to regard them as derivatives of the reticulo-endothelial system. According to this view they may be regarded as the homologues in the blood of the tissue histiocytes, and certainly the two classes of cells agree closely in their functional activities. Others, however, put monocytes in the lymphocyte class ; others, again, regard the bone-marrow as the chief site of their formation. As will be described below, the monocytes react to various chemotactic stimuli and occur in increased numbers in the blood in certain conditions, though the reaction is less rapid than in the case of the polymorpho-nuclears.

The formation of myeloid tissue in abnormal sites is an interesting phenomenon, though, as we have said, it is somewhat rare. It occurs more readily in infants, for example, in the liver and spleen in anæmias, in the pelvis of the kidneys in rickets, etc. ; but it has been found in the adult when the bone-marrow has been destroyed by new growth (p. 521), also within bone formed by a process of metaplasia in various sites. It is to be noted that the new tissue is the seat of erythroblastic as well as myeloblastic formation. In the lower animals the formation of myeloid tissue often occurs in the spleen in infections—myeloid transformation (p. 492). There is still difference of view as to how new myeloid tissue arises. Maximow, for example, regards most of the cells of the reticulo-endothelial system as potential hæmocytoblasts, capable of producing cells both of the erythroblast and myeloblast series. Potential foci of new blood formation are thus present in the adult not only in the spleen and lymphoid tissues but also in the hepatic sinusoids and though in less degree, in the ordinary connective tissues. Sabin, Cunningham and Doan, on the other hand, hold that the cells have two sources of origin, the erythroblasts being formed from the vascular endothelium, while the myeloblasts are formed extravascularly from reticulum cells. Still another view is that of Naegeli, according to which all the blood cells have a mesenchyme cell as their ancestor, with the exception of megaloblasts, which are derived from endothelial cells. While views differ as regards details, there is pretty general agreement amongst recent workers that certain cells of the reticulo-endothelial system have the faculty under certain circumstances of producing new groups of cells which afterwards undergo differentiation into the various cell types of myeloid tissue. In some of the acute forms of leukæmia, to be described below, when the proliferative process is carried far back in the ontogenetic tree, we meet with undifferentiated cells which may not be distinguishable by their histological characters. None of these facts, however, affect the general statement made above, namely, that when once the cells have become differentiated the various classes remain practically distinct.

Oxydase Reaction. It may be added that cells of the myeloid series contain certain enzymes not possessed by those of the lymphoid tissues. One of these is an oxidizing ferment or oxydase, whose presence can be shown by certain colour reactions, one of the most convenient in application being the production of indophenol, a dark blue substance, by the synthesis of alphanaphthol and para-dimethyl-phenylenediamine. When granular leucocytes in films are exposed to a mixture of the solutions of the two substances last mentioned, they assume a dark blue colour, owing to the formation of indophenol in their substance and on their surface. The reaction is given also by the myelocytes, and to a slight extent by the myeloblasts, although some of the latter may react negatively. The large mononuclears of the blood likewise give a slight oxydase reaction ; on the other hand, lymphocytes never give a positive reaction. The test has been of service in interpreting the nature of the cells in acute leukæmias, and it may be said that the cells giving a positive reaction are not of the lymphocyte class ; at the same time it must be borne in mind that some of the myeloblasts may react negatively. The granular leucocytes (at least neutrophiles) contain also proteolytic enzymes, to which the softening of the tissues in suppuration and the autolysis of tissues rich in these cells, are due. Such enzymes have not been found in lymphocytes.

Changes in the leucocytes in disease are of great variety, and we can give only the more important facts. The total number may be either increased or diminished and the terms *leucocytosis* and *leucopenia* are then applied respectively. Variations in the proportion of the different cells also occur, as shown by a differential count, and these may be met with whatever the total number of leucocytes may be. And further, cells not normally present, chiefly of the myelocyte series, may appear in the blood.

Neutrophile[1] or Ordinary Leucocytosis. The principles on which this is produced have already been explained (p. 132). The number of leucocytes per c.mm. may rise to 50,000 or even more, but such high figures are rare, and 20,000 to 25,000 may be regarded as a marked leucocytosis. The increase is mainly on the part of the polymorpho-nuclear leucocytes, which may number more than 90 per cent. of the total cells (Fig. 289). Varieties of leucocytosis are usually distinguished as (*a*) inflammatory or infective, (*b*) toxic, (*c*) cachectic, (*d*) post-hæmorrhagic, but they are not to be regarded as essentially different in nature.

Leucocytosis can be produced experimentally by the injection of definite chemical substances, e.g. peptone, bacterial toxins, essential oils, etc., but in infective leucocytosis also, the agents are chemical products of the bacteria, which act as chemotactic agents. Accordingly there is no essential difference between infective and toxic leucocytosis, although in certain diseases, e.g. diphtheria, toxæmia rather than infection is the outstanding feature. We may say that all inflammatory conditions which are characterised by an emigration of polymorpho-nuclear leucocytes, are attended by a blood leucocytosis. Thus it occurs in the various inflammatory conditions caused by the pyogenic organisms—in suppurations, in pneumonias, in erysipelas, etc., also in plague. In typhoid fever there is no such emigration of the polymorpho-nuclears, and in the blood the number of leucocytes is usually diminished, chiefly on account of a fall in the number of the polymorpho-nuclears. In acute miliary tuberculosis without complications there is no leucocytosis. This is the rule also in influenza, unless inflammatory conditions such as pneumonia are superadded; in measles and in undulant fever leucocytosis is generally absent. In many chronic wasting diseases, notably in cases of malignant disease of the alimentary canal, what is often called *cachectic leucocytosis* is present along with secondary anæmia. This may be regarded as a mild form of toxic leucocytosis. After a large hæmorrhage, leucocytosis—*post-hæmorrhagic*—appears within a few hours and then passes off in a day or two if the hæmorrhage is not repeated (p. 450). Further, there is evidence that a certain degree of leucocytosis may be produced by the absorption of the products of tissue disintegration. The leucocytosis met with in cardiac infarction is an example of such an occurrence.

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[1] The term 'neutrophile,' which is convenient, was originally applied by Ehrlich in view of the reactions given by the use of certain mixed stains. With the eosin-containing stains now ordinarily used an oxyphile reaction is given by the granules of the neutrophile leucocytes, though the colour is not quite of the same tint as that of the granules of the eosinophile leucocytes.

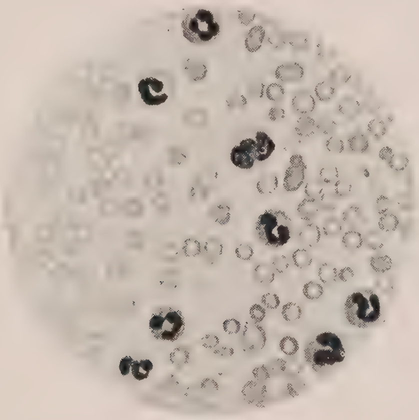

Fig. 289.—Blood with ordinary Neutrophile Leucocytosis.

Note the marked increase of polymorpho-nuclears. × 400.

The Arneth and Cooke-Ponder Counts.[1] A further analysis of the leucocytes may be made by studying the stage of development, i.e. the age of the cells. Two methods may be mentioned, that of Arneth and that of Cooke and Ponder. In the Arneth count, the leucocytes are arranged in five classes according to the number of lobes of the nucleus, the youngest cells having a simple nucleus, the next youngest two lobes, and so on; there are also sub-divisions in the classification. The Cooke and Ponder count depends on the fact that as a leucocyte ages, the nuclear lobes are connected at first by bands of chromatin and ultimately by filaments. The cells are arranged in five classes in ascending series from left to right—those with no filament, those with one, two, three, four filaments. In a normal blood the largest number of leucocytes is in class three. Both methods accordingly show the relative ages of the cells and especially those which have most recently left the bone-marrow. In all infections there is a greater proportion of these younger cells, that is, there is a shift to the left; the extreme result is the actual appearance of myelocytes in the blood. In some infections there may be a normal leucocyte count with increase in the proportion of young cells, and this may be sometimes of service in diagnosis in obscure cases. Cooke has found that in pernicious anæmia a shift to the right occurs, this indicating an abnormally high proportion of adult cells.

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[1] *The Polynuclear Count*, by W. E. Cooke and E. Ponder, London, 1927.

Eosinophilia. The increase of the eosinophiles in the blood proceeds on the same principles as ordinary leucocytosis, and it is usually met with where there is much local emigration of eosinophiles. It occurs in certain definite conditions, viz. :—

(*a*) In certain chronic skin infections, such as pemphigus, urticaria, psoriasis, etc., eosinophilia of moderate degree is usually present. An increase of eosinophiles, often met with in scarlet fever, probably belongs to the same category.

(*b*) In infestation with certain animal parasites, e.g. ankylostoma, filariæ, trichina spiralis, bilharzia, echinococcus the increase is often very marked; this is especially the case with nematodes, the percentage of eosinophiles in ankylostomiasis sometimes reaching 40 per cent. or even more (Fig. 290). The examination of the blood in such cases has accordingly a diagnostic importance.

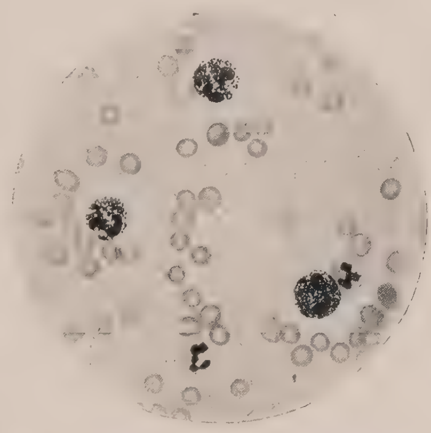

FIG. 290.—Eosinophilia in Ankylostomiasis; three Eosinophile and two Neutrophile Leucocytes are shown. × 400.

(*c*) In bronchial asthma, eosinophilia is usually present, and is to be related to the local emigration of eosinophiles in the bronchial tubes; it occurs also in hay fever. Both asthma and hay fever are anaphylactic conditions and these in general are accompanied by eosinophilia. It is possible that eosinophilia in skin diseases is, in part at least, of similar kind. The real nature of eosinophilia is not understood, but in a general way it appears to be induced by abnormal proteins and not directly by bacterial infection.

Further, in some cases of malignant diseases involving the marrow of bones, a considerable degree of eosinophilia has been observed. In leukæmia also, to be described below, there is often an increase of eosinophiles, and at the same time the eosinophile myelocytes may appear in the circulating blood.

The opposite condition, diminution in the eosinophiles, is often present in cases of acute infections with ordinary leucocytosis. In lobar pneumonia, for example, eosinophiles are practically absent, as a rule, during the period of fever ; and this may be followed by slight eosinophilia after the crisis. The eosinophiles are diminished in number along with the neutrophiles in aplastic conditions of the bone-marrow.

Lymphocytosis. This term is often used when there is a percentage increase of lymphocytes in the blood, that is, a *relative* lymphocytosis. As diminution in the number of leucocytes is generally due to a fall in the polymorpho-nuclears, it is accompanied by a percentage increase of the lymphocytes, and thus a relative lymphocytosis will occur in the various conditions of leucopenia mentioned below, pernicious anæmia, purpura, kala-azar, etc. A true lymphocytosis, that is, an actual increase in the number of lymphocytes per c.mm., is met with also, although it is not common. It is usually a marked feature in smallpox, especially in moderately severe cases where both the small and large lymphocytes are increased along with the mononuclears. An actual increase of lymphocytes is often present in the secondary stage of syphilis, that is, at a time when there are numerous foci of infiltration by these cells. Lymphocytosis is a distinct feature in glandular fever ; many of the cells may be of the large type and show abnormal characters (p. 505). It occurs also in whooping-cough, and is said to be not uncommon in chronic disturbances of the alimentary tract in childhood. In connection with this, however, it must be kept in view that normally the proportion of lymphocytes in the child is higher than in the adult. The number is highest shortly after birth and gradually falls in subsequent years ; allowance for this fact must accordingly be made in judging of increase or decrease of these cells. The outstanding increase of lymphocytes, however, is met with in the lymphatic form of leukæmia (p. 477), and a percentage increase of lymphocytes may sometimes be observed to precede the actual rise in the leucocyte count.

Increase of Mononuclears ; Monocytosis. The reaction of the mononuclear leucocytes occurs more slowly than that of the polymorpho-nuclears, and is met with in less acute conditions. Thus in an ordinary leucocytosis which has lasted some time, they may become actually and sometimes relatively increased, as is well exemplified in acute pneumonia about the time of the crisis. They react also in certain protozoal infections, e.g. malaria, trypanosomiasis, and kala-azar, in which diseases there is no increase of the neutrophiles. In chronic malaria, the presence of numerous mononuclears is often a striking feature, and some of them may contain small granules of pigment ; this condition comes to be of importance in diagnosis when parasites cannot be found. An increase of the mononuclears is usually associated with that of the lymphocytes in cases of smallpox. Monocytosis, sometimes of marked degree, occurs also in a form of angina—‘ monocytic angina ’ (Schulz).

The most remarkable example of monocytosis in relation to bacterial infection is that recorded by Murray, Webb and Swann. They found that a bacillus—*B. monocytogenes*, which they cultivated from an epizootic amongst rabbits, produced on experimental inoculation a marked reaction of the mononuclear leucocytes. In extreme examples these cells numbered fully 6,000 per c.mm. and their percentage reached over forty. Monocytosis has been also observed in tetrachlorethane poisoning, there being sometimes a progressive increase of monocytes up to a similar percentage (Minot and Smith).

It may further be added that a form of leukæmia has been recently recognised in which the cells in excess are monocytes—*monocytic leukœmia* (p. 481).

An important point is that in supravital staining by neutral red (a 1 : 10,000 solution in normal saline) the monocytes ingest the dye which forms numerous small segregation granules in the cytoplasm ; sometimes these granules are arranged in rosettes. Supravital staining again links the monocytes with the histiocytes although minor differences occur in the arrangement of granules. As stated above, the monocytes give a positive, though slight, oxydase reaction.

Leucopenia. This change, which means a leucocyte number below the normal, is met with in both acute and chronic conditions. Its occurrence in typhoid fever has already been noted, and sometimes in conditions which are usually attended by leucocytosis, an overwhelming infection leads to leucopenia. This is seen, for example, in some cases of acute pneumonia, especially in alcoholics ; and the absence of leucocytosis or the presence of leucopenia has a grave significance, and may be attended by the appearance of a few myelocytes in the blood. Leucopenia is met with in various anæmias and in many purpuric conditions. The number of leucocytes may sometimes fall in such conditions to 1,000 per c.mm., being associated with a relative lymphocytosis. Leucopenia may also result from the action of certain chemical poisons on the marrow. An interesting fact is that in anaphylactic shock a marked leucopenia is met with. This may occur with great rapidity, and is apparently due mainly to an accumulation of leucocytes in the capillaries of internal organs. Leucopenia usually representing as it does a deficiency in granular leucocytes is sometimes called agranulocytosis, but this term is generally applied to a special form, which may now be described.

Agranulocytosis. This is a condition in which there is a marked leucopenia with great diminution of the polymorpho-nuclears. Such a condition has in recent times been found to be especially associated with a severe inflammation of the fauces and gums, which may be followed by gangrene—*agranulocytic angina*. This affection has been met with chiefly in women and is attended by a high mortality. The blood shows a great diminution in the number of polymorpho-nuclears, these cells being often quite scanty. The erythrocytes and the platelets are usually not affected. Examination of the marrow has shown in most cases a practical absence of polymorpho-nuclears and sometimes also a great diminution of myelocytes which may be attended by degenerative changes in the cells. As a rule myeloblasts are abundant and there is no deficiency in the amount of marrow, but sometimes aplasia has been recorded. The essential change may thus be said to be a failure in the maturation of the myeloblasts with consequent deficiency in the supply of leucocytes to the blood.

It has been established that an abnormally low leucocyte account precedes the severe disease when infection of the throat or other region occurs. We may thus say that there is a pre-existing marrow abnormality evidenced by failure in the reactive production of polymorpho-nuclear leucocytes. The infection becomes more severe in consequence and in its turn acts injuriously on the marrow and increases the agranulocytosis ; a vicious circle is thus established. Sometimes a familial tendency has been observed. A very important fact is that in the large majority of cases the condition has followed the administration of certain synthetic analgesic drugs. Barbiturates were at one time believed to be the chief agents concerned, but it is doubtful whether they act by themselves, and it is now recognised that amidopyrine and allied compounds are chiefly concerned, though there are probably others ; e.g. dinitrophenol used in slimming, gold, sanacrysin, etc. It is to be noted that the effects of amidopyrine in susceptible individuals are different from those of simple poisoning with the drug. And another important point is that the dose sufficient to produce the disease in those susceptible persons may be relatively small, in fact a fraction of the poisonous dose. It is believed that sometimes a harmless dose may act as a sensitising dose, severe symptoms developing after another dose later. In cases where drugs are not concerned we must regard the disease as the effect of the infection itself acting on a marrow with want of reacting power. One cannot say whether or not this is an inborn idiosyncrasy.

The Presence of Myelocytes. The appearance of these cells in the blood has an important clinical significance. In addition to myeloid leukæmia, where their presence in large numbers along with myeloblasts is a prominent feature, they are met with in severe anæmias, e.g. in pernicious anæmia, but only occasionally and in small numbers. It is to be noted that they appear in the blood, more frequently in the anæmias of childhood than in those of adult life. A few myelocytes may be found also in some very severe infections, the most striking example perhaps being hæmorrhagic smallpox. In such conditions their appearance in the blood is probably due to damage done to the marrow by toxins, which allows their escape into the circulation ; it can hardly be regarded as a reactive phenomenon. It may be noted that in the various conditions mentioned where myelocytes are present in the blood, they are often accompanied by erythroblasts.

Another abnormal form of cell met with in infections and anæmias along with myelocytes is that called by Cooke the 'macropolycyte,' of which he describes two types. One resembles a polymorpho-nuclear leucocyte, but is considerably larger and has many nuclear lobes well separated from one another; he finds that it has no special significance. The other cell resembles a small megakaryocyte of the bone-marrow in the characters of its protoplasm and nuclear configuration. This cell appears to occur in the blood only a short time before death. It has thus a serious prognostic significance; in fact, its appearance in the blood may be regarded almost as an agonal phenomenon.

The Basophile Leucocytes. In myeloid leukæmia these cells sometimes take part in the leucocyte increase, their proportion, however, varying considerably; sometimes they are scanty, sometimes numerous. In the latter case, basophile myelocytes also may appear. In the blood in various chronic wasting diseases, an increase of basophiles may be occasionally met with, but it seems to occur in an irregular way, and there is no condition definitely known which calls forth a basophile leucocytosis. The granules of these cells usually give a metachromatic reaction, staining of a purplish tint, and the cells are known as 'mast-cells.' It is to be noted, however, that mast-cells are also met with in the tissues, and have probably a local origin. The view that the granules are composed of heparin has already been referred to (p. 89).

Blood Platelets. Variations in the number of platelets is of common occurrence in conditions of disease. Increase is the rule in chronic conditions where there is leucocytosis, especially when associated with anæmia, e.g. malignant disease, chronic suppuration, etc. In acute leucocytosis, however, the number may not be raised. Such increase of platelets may conveniently be called *thrombocytosis* and it has merely a symptomatic significance. In most of the anæmias where there is leukopenia the platelet count is reduced and may be markedly so, e.g. in pernicious anæmia, aplastic anæmia, etc. In chronic myeloid leukæmia the number may be very high; we have seen over 1,000,000 per c.mm. in one case. On the other hand, in the lymphatic and acute types of the disease, scarcity of platelets is the rule.

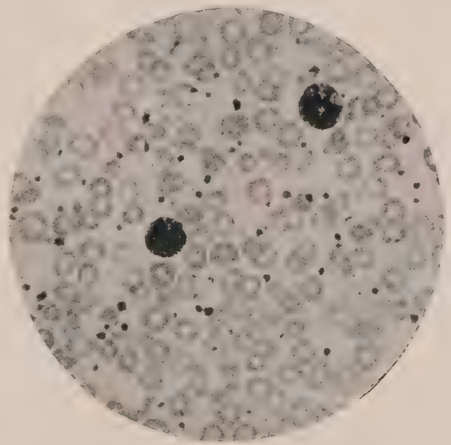

Fig. 291.—Blood in thrombocythæmia showing great increase of platelets, regularly distributed. (The number was over 3,000,000 per c.mm.) (Dr. J. Reid.) × 500.

There are, however, conditions in which there is some fundamental abnormality in platelet formation. A very low count is a feature in one form of purpura—accordingly called thrombocytopenic purpura—which will be described later. Then there is a very rare form of disease in which the platelet count is very high, a count of over 3,000,000 per c.mm. having been observed (Fig. 291). This condition is associated with a tendency to thrombosis and hæmorrhage, and the disease is known as hæmorrhagic thrombocythæmia. Its causation is unknown, but a great increase of megakaryocytes in the bone-marrow has been observed (J. Reid). A further abnormality in platelets has been observed, namely in hæmophilia, where there is an increased stability so that they break down in shed blood more slowly than normally (p. 484).

TYPES OF ANÆMIA

A detailed classification of the anæmias would hardly be helpful at this stage, but the following, which is an abridgment of Cappell and McCluskie's classification, will give a general survey of the chief factors concerned.

I. Post-hæmorrhagic Anæmia—acute or chronic.

II. Dyspoietic Anæmia, characterised by marrow hyperplasia, but with deficient output of erythrocytes.

(*a*) *Megalocytic anœmia*, due to want of the hæmopoietic factor in the liver necessary for normal blood formation.

(*b*) *Microcytic anœmia*, due to deficiency in intake or utilisation of iron, or of vitamin C, thyrotoxin, etc.

III. Hæmolytic Anæmia due (*a*) to congenital or constitutional abnormality, or (*b*) to toxin action.

IV. Aplastic Anæmia due (*a*) to congenital or constitutional abnormality, or (*b*) to toxic action.

This scheme will not be strictly followed, but the various types of anæmia to be described readily fall into one or other of these categories and the different factors concerned in the production of each will be considered.

Post-Hæmorrhagic Anæmia. The restoration of the fluid part of the blood after hæmorrhage has already been dealt with (p. 53); it of course leads to a dilution of the blood with accompanying fall in the number of erythrocytes per c.mm. The first evidence of regeneration of red corpuscles after a large hæmorrhage, is a progressive increase in the number of reticulocytes, and the degree of increase is an indication of hæmopoietic activity. They show, as has been explained above, a varying degree of polychromasia in ordinary films. Along with them a few normoblasts may be present, and, if there are repeated hæmorrhages, they may become fairly abundant. As regeneration becomes complete the reticulocytes return to their normal level and normoblasts gradually disappear. These are the essential changes indicating regeneration, and they are to be related to active proliferation of erythroblasts in the bone-marrow, which come to form a larger proportion of the cellular elements of the marrow than normally. A polymorpho-nuclear leucocytosis of moderate degree appears within a few hours after hæmorrhage; it passes off in two or three days, and the leucocytes remain normal unless the hæmorrhage is repeated.

In certain conditions, e.g. severe epistaxis, repeated bleeding from gastric ulcer, piles, or tumours of various kinds, etc., a *chronic* anæmia of severe type may result. The most striking examples used to be met with in cases of bleeding uterine myomata, and the anæmia was sometimes extreme. This, however, is now comparatively rare, owing to operative treatment. In chronic post-hæmorrhagic anæmia the number of red corpuscles may occasionally fall to a million per c.mm. or even lower. The corpuscles come to vary considerably in size, the smaller forms predominating ; there may be a considerable number of poikilocytes, while a few normoblasts may be present. The red corpuscles appear paler than normal, and the colour index is reduced in a moderate degree, though not so much as in primary microcytic anæmia.

The process of regeneration after one or two large hæmorrhages is relatively a rapid one, and in the human subject a million corpuscles per c.mm. or more may be added within a week. But when the anæmia has existed for some time owing to repeated hæmorrhages, regeneration occurs much more slowly. In cases of hæmorrhage, especially when it has been oft repeated, an erythroblastic reaction occurs in the bone-marrow. This is shown by a proportionate increase of the red marrow in the small bones and also by an extension of the red marrow into the shafts of the long bones ; whilst throughout the marrow there is a proportionate increase of erythroblasts which may be in large numbers (Fig. 292). Experiments on animals have shown that blood regeneration is more rapid after destruction of blood corpuscles by a hæmolytic poison than after hæmorrhage, and this is apparently due to the fact that in the former case iron and possibly other substances used in the formation of red corpuscles, are retained in the body.

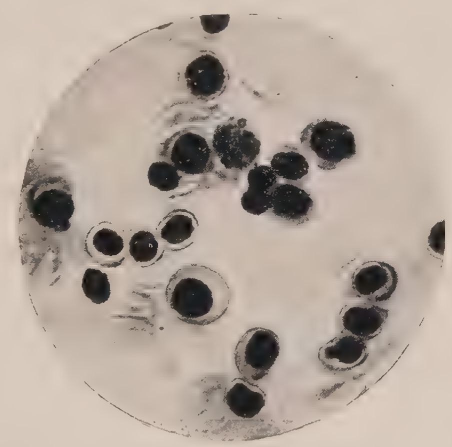

Fig. 292.—Film of Marrow of Rabbit, showing Erythroblastic Reaction after Hæmorrhage. A group of erythroblasts is shown. × 1,000.

‘ **Secondary Anæmia.**’ This term has now largely fallen into disuse. It was formerly applied to anæmia resulting from various types of organic disease such as malignant disease, chronic suppuration, chronic Bright’s disease, etc. Whilst it has not a definite place in modern hæmatological schemes, it had the advantage of emphasising the fact that anæmia may be the result of organic disease outside the hæmopoietic system. To speak generally, the blood changes correspond more or less closely with those in chronic post-hæmorrhagic anæmia, with the exception that signs of regeneration are deficient. The number of red cells is as a rule only moderately reduced, but in some cases, e.g. carcinoma of the stomach, it may fall to a low level. The anæmia is microcytic and hypochromic, but not in marked degree. Reticulocytes are usually scanty, as are also normoblasts. There is usually a distinct leucocytosis of neutrophile type and the number of blood platelets is increased, sometimes markedly so (Fig. 293). In most cases the fault is chiefly one of formation of erythrocytes, but in some a hæmolytic factor is concerned, e.g. in streptococcal cases.

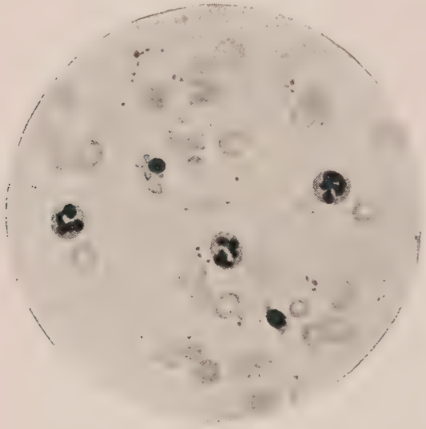

Fig. 293.—Film of Blood in Secondary Anæmia, showing pale Corpuscles of varying size, most being undersized, also Poikilocytes; the Platelets are numerous (compare with Fig. 294). × 400.

MEGALOCYTIC (HYPERCHROMIC) ANÆMIA

Pernicious anæmia is the outstanding example of this type but there are other diseases in which the same abnormality in blood formation is present.

Pernicious Anæmia.[1] This affection used to be known also as *essential* or *idiopathic anæmia.* It is mainly a disease of late adult life and affects the sexes with about equal frequency, being, however, rather commoner in men than in women; in the latter it tends to occur at a somewhat earlier period. It is sometimes, though very rarely, met with in young adults. There is intense pallor of the skin and mucous membranes, attended often with a lemon tint of the former; on the other hand there is, as a rule, little or no emaciation. Up till the recent introduction of treatment with liver, pernicious anæmia was usually a progressive disease and led to a fatal termination, although remissions were not uncommon and sometimes marked improvement took place. The disease has now become relatively amenable to treatment (*vide infra*). It was described first by Addison and is thus often called *Addisonian anæmia.* It is now to be regarded as a *megalocytic* and *hyperchromic* anæmia resulting from a deficiency of the so-called ‘intrinsic factor’ in the gastric secretion (p. 459).

Condition of the Blood. The blood is very pale in colour and distinctly watery, and coagulation occurs slowly. The number of red cells is greatly reduced, not infrequently being below 1,000,000 per c.mm., and may fall to less than half that figure before death. The colour index, that is the average amount of hæmoglobin per corpuscle, is raised, being often 1·1 or higher, and the individual corpuscles are well coloured. There is usually, though not always, great variation in the shape of the corpuscles, numerous poikilocytes being present, and the corpuscles have little tendency to form rouleaux. While the size varies greatly, the presence of a large proportion of megalocytes is usually a marked feature (Fig. 294), and the average size of the corpuscles is distinctly above normal (Price-Jones). In stained preparations, some of the corpuscles usually show polychromatophilia (p. 437), and punctate basophilia may be associated with it. The number of reticulocytes varies considerably according to the progress of the disease; in the stage of relapse it is usually about 3 per cent. (Davidson and Gulland). Nucleated red corpuscles can in general be found, and sometimes occur in considerable numbers. They may be both of megaloblastic and normoblastic type, and often show considerable variety in the configuration of their nuclei (p. 439). The presence of megalocytes and megaloblasts along with a high colour index, is thus an important feature of this type of anæmia (Fig. 295). Cabot's 'ring-bodies' are sometimes present (p. 439). The *leucocytes* are, as a rule, reduced in number, being not infrequently about 2,000 per c.mm., and the decrease is mainly on the part of the polymorpho-nuclear cells, which may be relatively scanty. There is often an increased proportion of the older leucocytes with lobes well separated—'a shift to the right' (Cooke) (p. 444). In some cases the leucocytes present are of normal type, but sometimes a few myelocytes and intermediate cells are present. The *blood platelets* also are reduced in number, and are often very scanty. Thus while the chief changes are in the erythrocytes, the diminished number of leucocytes and of platelets is a striking feature and is another evidence of disturbed marrow activity.

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[1] See *Pernicious Anæmia*, by L. S. P. Davidson and G. Lovell Gulland, London, 1930; *The Anæmias*, by Janet M. Vaughan, London, 2nd edit., 1936; *Pathological Physiology and Clinical Description of the Anæmias*, by W. B. Castle, G. B. Minot, and H. A. Christian, New York, 1936.

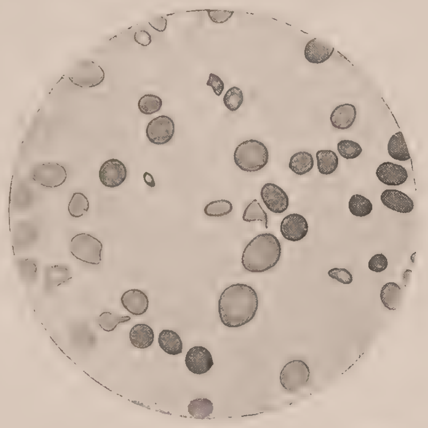

FIG. 294.—Blood in Pernicious Anæmia showing numerous Poikilocytes and variations in the size of the Corpuscles. × 400.

The above is a general account of the blood picture, but variations are met with and some of these are of clinical importance. The number of reticulocytes and polychromatophile cells supplies valuable evidence of regenerative activity, but it should be taken as only a *relatively* favourable phenomenon, since the course of the disease depends on the amount of blood destruction as well as of blood formation. Occasionally a large number of reticulocytes and erythroblasts may appear in the circulation, this constituting a ‘ blood crisis,’ and usually indicating a special degree of regenerative activity. It should be borne in mind also that sometimes shortly before death, numerous erythroblasts may be present in the circulation, the phenomenon in this case having a different significance (p. 440). In some cases, erythroblasts are practically absent throughout the disease, and there is often associated a great diminution in the number of polymorpho-nuclear leucocytes. There is a lack of evidence of activity of the bone-marrow, and, as a matter of fact, with the conditions mentioned, the marrow is often to be found in an aplastic state (*vide infra*). Such cases are, however, rare.

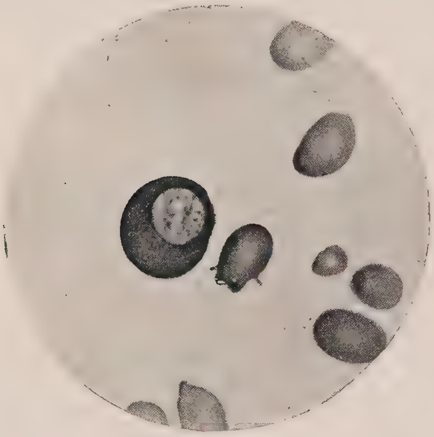

Fig. 295.—Blood in Pernicious Anæmia, showing a Megaloblast and Poikilocytes. (J. S. D.) × 1,000.

In pernicious anæmia, bilirubin is increased in the plasma and gives an indirect van den Bergh reaction. The amount will depend on the stage of the disease, but during a severe relapse it may rise to 3 units or even higher. Marked increase is accompanied by an increased depth of the yellow colour of the serum. The ‘ icteric index ’ is likewise raised. The urine is often dark in colour and may contain a considerable amount of urobilin and urobilinogen.

Changes in the Organs. These are manifold in character, some being related to the essential nature of the disease, others being merely secondary to the anæmia.

In the *bone-marrow* very important changes are present. The fatty marrow of the long bones is replaced, to a varying extent, by a red cellular marrow of dark colour (Fig. 296). The femur is usually the bone examined and in it the change starts at the upper end and extends downwards. The whole medullary cavity may ultimately be occupied by red marrow and there is often a considerable absorption of bone trabeculæ, so that portions of marrow can readily be cut out.

On microscopic examination the condition is found to be one of *megaloblastic hœmopoiesis.* There is a large proportion of megaloblasts and their more primitive predecessors with basophile cytoplasm. The proportion of the two classes of cells varies much. Sometimes the megaloblasts are very numerous but they may be scanty. Their cytoplasm may be eosinophile or show varying degrees of polychromasia. The nucleus may show a fine reticular structure but is often pyknotic and fragmented. Some megaloblasts may be much larger than any found in the blood and the term 'gigantoblasts' (Fig. 298) has been applied to them. Normoblasts are scanty. Myelocytes are usually diminished in number but they may be in quite large proportion, and then the paucity of polymorphs in the blood may result from defect in the maturation of myelocytes. Megakaryocytes are usually quite scanty and may be absent from large areas of the marrow. It is thus seen that although the marrow is hyperplastic there is a deficiency in the normoblastic formation of erythrocytes. Megalocytes are produced but the supply of them is insufficient to maintain the erythrocyte count and there is evidence that they undergo an early destruction in the blood.

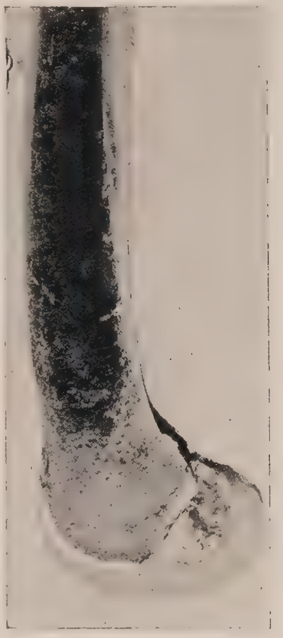
FIG. 296.—Section of Femur in Pernicious Anæmia, showing the dark red marrow throughout the shaft.

Within the marrow there is also evidence of the excessive destruction of red corpuscles —phagocytosis of these and accumulation of hæmosiderin granules in the reticulo-endothelial cells. The amount, however, varies greatly, depending probably upon the amount of recent blood destruction.

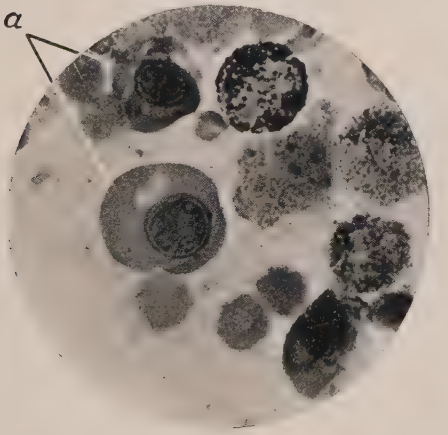

FIG. 297.—Film of Bone-marrow from a case of Pernicious Anæmia, showing (a) large Megaloblasts. (J. W. S. B.) × 1,000.

Sometimes, however, the marrow reaction does not occur or is feeble. The marrow of the long bones remains yellow, or there may be small islets of reddish marrow here and there, whilst the marrow in the short bones is not increased and may be even in defect. Erythroblasts are scanty and myelocytes have been found to be diminished, many of the cells being of the myeloblast type. When this condition is present, the term *aplastic* type is given, though we do not know the factors determining its occurrence.

Alimentary System. W. Hunter laid special emphasis on lesions of the mouth, especially glossitis with formation of small vesicles and ulcers, followed by atrophic changes. The tongue has often a red and raw appearance. But such lesions are not always present and are not special to the disease; they occur also in microcytic anæmia and in sprue. The essential defect in pernicious anæmia lies in the *stomach* and results in the absence of the intrinsic factor presently to be considered. As yet it is not possible to relate this to a specific cellular change. Meulengracht has found that in the pig the chief site of production of the intrinsic factor is the pyloric segment of the stomach. On the other hand, in pernicious anæmia he found that the chief change was in the fundus, as also did Magnus and Ungley, there being in that region a marked atrophy affecting all the coats. Further observations are necessary. Achlorhydria is practically always present and is usually associated with *achylia gastrica*—complete absence of the digestive ferments. Such defects, however, may be met with in other conditions (p. 462). They have in some instances been found to precede the onset of pernicious anæmia and they are not affected by liver treatment. The presence of achlorhydria results, of course, in a loss of the normal antiseptic action of the gastric juice. On the one hand, organisms from the mouth are able to survive and multiply in the stomach after being swallowed, and, on the other hand, there is an extension upwards of the bacterial flora in the large and small bowels. In this way, secondary effects may be brought about.

There is also deposit of hæmosiderin in various organs. The *liver*, generally a little enlarged, has usually a ground-work of chocolate-brown tint, against which the central parts of the lobules, fattily degenerated and free from pigment, stand out. It gives a marked iron reaction with the usual reagents, the colour being deepest at the periphery of the lobules. The hæmosiderin granules are present in the liver cells in the outer two-thirds of the lobules, being most abundant round the portal tracts, and are situated chiefly in the axial part of the trabeculæ, that is, round the bile capillaries; some may be present also in the Kupffer cells throughout the lobules. There may be islets of intravascular formation of megaloblasts (Piney). The *spleen* varies in size, but is usually not much enlarged and may be of normal size; it is of dark red colour and gives an iron reaction of varying degree in different cases. The hæmosiderin occurs in somewhat coarse granules, and is contained mainly within cells in the pulp, the Malpighian bodies being free. Sometimes phagocytosis of red cells is present, but it is usually not a prominent feature. Myeloid transformation in varying degree may be present. The size of the spleen would appear to depend chiefly upon the activity of blood destruction going on. Enlargement has been found especially during the stage of relapse. The condition of the *kidneys* varies considerably. Sometimes they contain a large amount of hæmosiderin which occurs as fine granules within the cells of the excreting tubules, appearing first and being most marked in the proximal limbs, whilst the glomeruli are free. Sometimes, however, the hæmosiderin is relatively scanty. Diffuse fatty degeneration is usually present in the tubules. The variations in the amount of hæmosiderin in the kidneys are of a striking character. Experiments by J. S. Young and myself have shown that a large amount of hæmosiderin may accumulate in the excreting tubules as the result of hæmoglobinæmia, even when it is insufficient to cause hæmoglobinuria. Accordingly, a minute degree of hæmoglobinæmia going on for some time *might* account for the large deposit occasionally met with in pernicious anæmia, but its occurrence has not been demonstrated.

The deposits of hæmosiderin and the increased bilirubin in the blood are to be taken as evidence of abnormal and excessive blood destruction. There has been a tendency on the part of some recent writers to overlook the hæmolytic factor but no one who considers the condition of the kidneys in some cases can doubt its importance. The amount of hæmosiderin occasionally present is remarkable. I have met with an equal degree only in long-standing paroxysmal hæmoglobinuria.

Other Changes. Marked fatty degeneration is present in the various organs, and is specially noticeable in the heart muscle, where it has a patchy distribution (p. 329). Capillary hæmorrhages or petechiæ are present often in the serous membranes, leptomeninges, and especially the retinæ, rarely in the skin. Occasionally the extravasations are of larger size. Such hæmorrhages are no doubt due to nutritional changes in the vascular endothelium, though not necessarily of a fatty nature. It may be added that in pernicious anæmia changes are sometimes present in the spinal cord, constituting subacute combined sclerosis (p. 779), and that these may give rise to a variety of symptoms, disturbances of sensation and motion, ataxia, etc. Such lesions are present in 5 or more per cent. of the cases, but in addition minor nervous disturbances, chiefly of a sensory nature, are common, and have been found to be due to peripheral neuritis. The three conditions of achlorhydria, subacute combined sclerosis and pernicious anæmia, represent the results of gastric defects. All may be present together or the achlorhydria may be accompanied by one of the two others ; there are also definite familial relationships between the defects. The etiology of the nerve lesions in pernicious anæmia is not definitely known but they are probably produced by the absence of a neurotrophic factor in the gastric juice, possibly an enzyme, which is different from the intrinsic factor of pernicious anæmia. Further investigation is, however, necessary.

The excessive diminution in the total hæmoglobin, with a corresponding diminution in the oxygen capacity of the blood, is an all-important change in pernicious anæmia. There is, of course, no diminution in the oxygen saturation of the arterial blood, but the amount of oxyhæmoglobin in the capillaries is greatly lessened and the oxygen supply to the tissues is thus interfered with—in other words, an anæmic anoxæmia results (p. 16). The oxyhæmoglobin in its passage through the capillaries is reduced to an abnormal degree and thus the amount of oxygen unsaturation of the venous blood is markedly increased. Although readily suffering from breathlessness on exertion, very anæmic patients do not tend to suffer from cyanosis and it has been stated that when the percentage of hæmoglobin (p. 18) falls below 25 per cent. of the normal, cyanosis cannot occur. The fatty degeneration which is so marked a feature in pernicious anæmia is apparently to be ascribed to the anoxæmia.

NATURE OF THE ANÆMIA. The establishment of definite knowledge on this subject, dates from 1926 when the efficiency of liver treatment of the disease was discovered by Minot and Murphy. The main facts with regard to this may first be given and then the pathology of the disease considered in the light of these results.

The discovery of the remarkable effect of liver was led up to by the work of Whipple and others with regard to diets most favourable for blood regeneration after hæmorrhage, one result being that the liver was specially efficient. The fundamental discovery of Minot and Murphy was that the administration of mammalian liver in cases of pernicious anæmia leads to what amounts to cure in a very large proportion of cases. The liver is effective when given in the raw or slightly cooked state ; prolonged cooking impairs somewhat its effect. A little later an efficient watery extract of liver was prepared by Cohn, and, since that time, a number of preparations have been introduced, some of which are suitable for intravenous or intramuscular administration. The active substance in liver has been found to be of non-protein nature, but its exact composition has not been determined —it is known as the *anti-anæmic* or *hæmopoietic factor* ; also, conveniently as the P.A. factor. Its administration in any effective form leads to a remarkable change. Within a few days the number of reticulocytes in the blood may rise from a previous 1 per cent. to about 25 per cent. or higher, the maximum number appearing usually in 8–12 days. And further, not only is there something like a stimulus to erythrogenesis but also a change from the megaloblastic to the normoblastic type. This has been clearly shown by examination of the marrow by sternal puncture during life. Frequently, in the course of two or three months the number of red corpuscles may rise practically to normal. At the same time, evidences of abnormal blood destruction disappear, the amount of bilirubin in the blood falling to normal. Abnormalities in the leucocytes also disappear. The achlorhydria, however, is not affected.

The essence of pernicious anæmia being the absence of a substance stored in normal liver and, to a less extent, in other organs, the question is carried a step further back, i.e. as to the origin of the defect. It cannot be due to the achlorhydria in itself as this is common in patients with normal blood formation. The work of Castle and his co-workers has supplied results of highly suggestive character. They found that when beef muscle is digested with normal gastric juice outside the body, the anti-anæmic factor is formed, as can be shown by tests on pernicious anæmia patients. The formation of the specific substance is due neither to the hydrochloric acid nor to the pepsin but to another unknown agent, probably an enzyme, as it is destroyed at 75° C. This agent was called by Castle the ‘ intrinsic factor ’ in contrast to the ‘ extrinsic factor ’ in muscle; it produces its effect in a neutral medium. Another important observation is that muscle digested with the gastric secretion from a case of microcytic anæmia with achlorhydria, is effective in bringing about the reticulocyte response in a patient with pernicious anæmia. These results thus show that the defect in pernicious anæmia is clearly the absence in the gastric juice of the intrinsic factor which is necessary for the formation of the anti-anæmic factor contained in liver. There is, of course, no defect in the absorption of the latter when formed, as is shown by liver treatment. The results harmonise well with what is known as to the frequent association of the disease with various gastric and intestinal lesions, as already described. Thus there would be an increased likelihood of pernicious anæmia developing in connection with gastric lesions, but the disease would not appear unless absence of the essential intrinsic factor had resulted.

Though pernicious anæmia is ordinarily due to absence of the intrinsic factor, it might theoretically result from failure of absorption of the P.A. factor from the alimentary tract, or from inability to utilise P.A. factor stored in the liver. There is evidence that both of these possibilities may actually occur.

Observations on the distribution of the extrinsic factor present in beef muscle have been published by Strauss and Castle. They found that it is absent in glutein, casein, nucleic acid, etc., but it is abundant in autolysed yeast (‘ marmite ’), in which its concentration is about twenty times that in muscle. Earlier observations pointed to vitamin B_2 being the extrinsic factor but this has not been established. None of the B vitamins have been shown to possess the characteristic therapeutic effect produced by the hæmopoietic principle in marmite (Wills). At present, the real nature of the extrinsic factor is not known. Davidson and Gulland have laid stress on constitutional or hereditary factors as playing an important part in the development of the disease, and there are many facts in support of this view. The disease has been found to affect more than one member of a family (blood relations) in a large number of instances, and, further, the incidence of achlorhydria has been found to be higher in such families than in the ordinary population. It is a point of interest too that pernicious anæmia has been observed in identical twins. No doubt there are all degrees of deficiency of intrinsic factor, and the deficiency may possibly be accentuated by external circumstances, pernicious anæmia thus resulting.

Other Forms of Megalocytic Anæmia. As a rule pernicious anæmia appears as a disease without any previous abnormal condition being known, but an anæmia with similar blood picture is related to other morbid states. Since it has been found that several of these are amenable to treatment with extrinsic factor alone, the term " megalocytic anæmia " is preferable. The first of these anæmias to be recognised was that due to infestation with the *Dibothriocephalus latus*, in which the changes in the blood, bone-marrow, etc., are similar to those in pernicious anæmia. It was for a time believed to be due to a toxin formed by the parasite, but its etiology is now recognised to correspond with other forms of megalocytic anæmia. More recently it has been recognised that a similar anæmia is not uncommon in sprue, and is occasionally met with in idiopathic steatorrhœa (cœliac disease). It has been observed after operations on the stomach, e.g. gastroenterostomy and gastrectomy, and in gastric carcinoma, although in these conditions a microcytic anæmia is the more frequent type. Megalocytic anæmia, sometimes of severe type, has been observed as a rare occurrence in connection with pregnancy. Spontaneous recovery sometimes follows delivery of the child. The microscopic

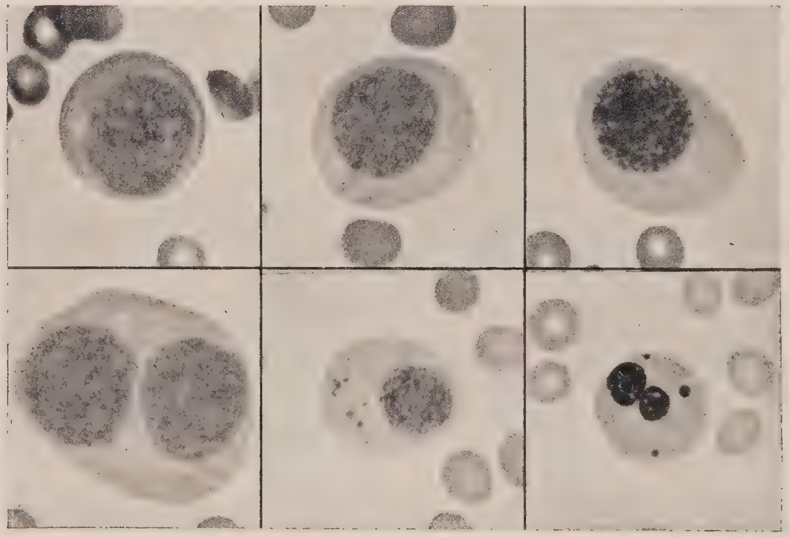

Fig. 298.—Megaloblasts as seen in bone-marrow obtained by sternal puncture in a case of megalocytic anæmia of pregnancy. *a*, *b*, *c* show transitions from (*a*) basophile megaloblast to (*c*) hæmoglobinised megaloblast ; (*d*) gigantoblast ; (*e*) smaller megaloblast with chromatin granules ; (*f*) megaloblast with fine basophile strippling. (D. F. C.) × 1000.

changes in the marrow found in such a case on sternal puncture may be of striking nature, as shown in Fig. 298. There is also a tropical megalocytic anæmia. It is a fact of importance, however, that in most of these examples the extrinsic factor in the form of marmite (autolysed yeast) brings about a striking remission with reticulocyte response. This shows that the intrinsic factor of Castle is not absent, though it may be deficient ; but further knowledge on this point is needed. In such cases there may be a lack of extrinsic factor in the food or, on the other hand, there may be a lack of absorption owing to the condition of the alimentary tract. Again, in the conditions mentioned there may be no evidence of increased hæmolysis as indicated by the amount of bilirubin in the blood ; the van den Bergh reaction is often negative. So far as present knowledge goes, we may say that megalocytic anæmia may be due either to absence of the intrinsic factor in the stomach of the patient or to absence of the extrinsic factor in the food, that is deficiency in sufficient amount.

MICROCYTIC (HYPOCHROMIC) ANÆMIA

The two chief examples are (*a*) idiopathic microcytic anæmia and (*b*) chlorosis, both affecting specially women, but the latter has now become very rare. Microcytic anæmia is met with also in infants under unsuitable nutritional conditions. The cause is deficient intake of iron or deficient absorption. In splenic anæmia the blood picture is of the same type and the disease has been included for convenience, though it is of quite different etiology.

Idiopathic Microcytic Anæmia. This is a name applied to a type of anæmia which has received recognition only in recent years. It has also been called simple achlorhydric anæmia (Witts), hypochromic anæmia with achlorhydria, achylic chloranæmia, etc. It is a disease mainly affecting women during the reproductive period, tending to be aggravated by pregnancy and often disappearing after the menopause. A small proportion of cases have been observed in men. The anæmia is of the microcytic or chlorotic type. The fall in the red corpuscles is usually not great but the colour index is lowered, sometimes to 0·5. The red cells are distinctly below the normal in size ; many of them show ring-staining owing to deficiency in hæmoglobin, but some of normal appearance are orthochromic (Price-Jones) (Fig. 299). Poikilocytes are scanty and erythroblasts are rarely found. The leucocyte count may be normal or there may be a slight leucopenia. The platelets usually give a low normal count. The defect is thus seen to be chiefly in the quality of the erythrocytes —they are undersized and deficient in hæmoglobin. The blood gives a negative van den Bergh reaction and there are no other signs of hæmolysis. The red marrow examined in a few cases has shown a degree of hyperplasia of the normoblastic type. This fact is of importance as showing that increase of normoblasts may be associated with deficient formation of erythrocytes, there being a failure to produce the final product. The spleen, as a rule, is moderately enlarged and may be palpable. In a certain proportion of cases the nutrition of the nails is affected; they are hollowed and fibrous—a condition of koilonychia.

As in pernicious anæmia, achlorhydria is a striking feature; Witts found it in 88 per cent. of his cases. In fact, it would appear probable that cases with the blood changes, but without achlorhydria, may be in a different category. It is to be noted that the gastric juice contains the "intrinsic factor", the absence of which causes pernicious anæmia. It also contains pepsin, though often in diminished amount. Glossitis with redness and soreness of the tongue is fairly common and digestive disturbance is usually present. Sometimes there is dysphagia, which is now usually attributed to contraction of the crico-pharyngeus muscle or at least to its non-relaxation during the act of deglutition. The association of the three symptoms, anæmia, glossitis and dysphagia, was recorded by Kelly and Paterson in 1919 and may suitably be called the Kelly-Paterson syndrome. (It is, however, usually spoken of as the Plummer-Vinson syndrome.) The dysphagia depends on structural changes, both hypertrophic and atrophic, in the epithelium of the mouth, pharynx and œsophagus, those giving rise to spasm in the post-cricoid region. Carcinoma sometimes supervenes in this part of the œsophagus (p. 526). For the reason stated, treatment with liver, which is so effective in pernicious anæmia, is without effect in microcytic anæmia. On the other hand, cases of the latter disease are very amenable to treatment with large doses of iron. The abnormalities in the blood disappear and there is a marked general improvement; the condition of achlorhydria, however, still persists. As with pernicious anæmia, a familial element has been observed in a proportion of cases.

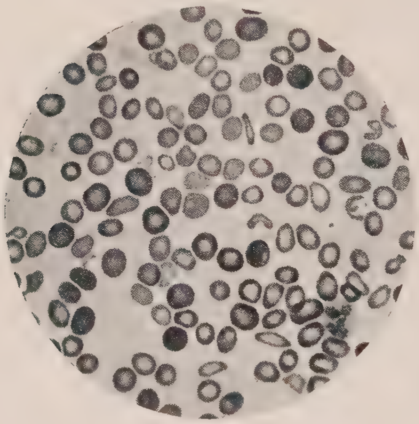

Fig. 299.—Film of Blood from a case of Microcytic Anæmia. Some of the red corpuscles show ring-staining owing to deficiency in hæmoglobin, others are larger and uniformly stained. (*Cf.* Fig. 284.) (J. A. W. McC.) × 400.

Chlorosis. This is a distinct type of anæmia affecting females in early adult life, and occurring especially soon after puberty. Chlorosis used to be a very common affection but it has now become quite rare. This change is one of the most remarkable facts in clinical medicine, but has received no satisfactory explanation. In chlorosis there is marked pallor of the skin and mucous membranes, associated with breathlessness on exertion, palpitation, and often constipation and amenorrhœa. There is no emaciation as the result of the disease : in fact the patients are usually well nourished so far as amount of fat is concerned. There is rather an excess than a diminution of gastric hydrochloric acid, and gastric ulcer used to be not infrequent. As regards the blood, the most characteristic feature is the marked reduction in the percentage of hæmoglobin. The colour index is markedly reduced and sometimes is below 0·5. As a result of the scanty hæmoglobin, the corpuscles in stained films may show only a ring-like staining at their margin. The red cell count usually shows some reduction, but a count below 3,000,000 per c.mm, is rather infrequent. The corpuscles tend to be pale and under-sized, and poikilocytes are occasionally met with and may be numerous ; normoblasts may be present but are rare. The number of leucocytes is sometimes normal but is usually reduced, the polymorpho-nuclears being specially affected, so that there is a relative lymphocytosis. The blood platelets as a rule show distinct increase, and this has been considered by some to have a bearing on the tendency to thrombosis which sometimes occurs. The disease is very amenable to treatment with iron. Lorrain Smith found by means of the carbon-monoxide method that the blood volume in cases of chlorosis was greatly increased, sometimes to twice the normal, so that the total amount of hæmoglobin in the blood might not be decreased ; and that this condition of hydræmic plethora disappeared with the cure of the disease by the administration of iron. The beneficial effect of the administration of iron preparations may be regarded as one of the characteristics of the disease.

The cause of chlorosis is unknown, though it seems in some way related to the establishment of the menstrual function ; beyond this it is not possible to say anything definite. Constipation and auto-intoxication have been considered by some to play a part, but cannot be regarded as more than favouring conditions. There is no evidence of increased blood destruction and the defect is apparently one of blood formation.

The Anæmia of Ankylostomiasis. In the anæmia produced by the *Ankylostoma duodenale*, the changes in the red corpuscles and hæmoglobin are of the chlorotic type, as have just been described, and it was found by Boycott and Haldane that the blood volume is increased as in chlorosis. For this reason they considered that the anæmia was not simply the result of loss of blood from the bites of the worms, as was generally supposed. Stockman found, however, that there was a diminution of iron in the liver, such as occurs after hæmorrhage, and there is no doubt that loss of blood plays a part in causing the anæmia. In ankylostomiasis a very important point is the presence of eosinophilia. The total number of leucocytes per c.mm. is usually about normal or somewhat increased, but the proportion of the eosinophiles is markedly raised, sometimes to 40 per cent. or even more. This eosinophilia is, of course, of importance as suggesting the possibility of a parasitic infection, though the finding of the ova of the parasites is the only certain means of diagnosis.

Ankylostoma duodenale. This parasite is a small nematode worm, the male being about 9 mm. in length and 0·5 mm. in thickness, the female being somewhat longer and thicker. The male is characterised by the presence at the posterior end of an umbrella-shaped copulatory bursa. The mouth possesses two pairs of teeth and a pair of lancets, and by means of these the parasite becomes attached to the intestinal mucous membrane. The parasites, both male and female, may occur in large numbers in the upper part of the jejunum. The females produce oval eggs with blunt extremities enclosed within a chitinous shell, about 60 μ in length; as met with in the fæces, the eggs usually show a four-celled segmentation stage (Fig. 363, i). Further development takes place, resulting in the production of a small larva which bursts the shell and escapes. The larvæ are about 0·25 mm. in length and have a needle-like shape. Infection of the human subject may occur by ingestion or directly through the skin. The latter mode of infection was worked out by Looss, who showed that the larvæ penetrate the skin often by the hair follicles, giving rise to itching which is sometimes attended by papular or vesicular eruption. They then make their way into the blood stream, partly directly and partly by way of the lymphatics and thoracic duct, and then pass to the lungs, where they become arrested and emigrate into the alveoli. Afterwards they ascend along the walls of the respiratory passages to the larynx and then pass down the œsophagus; having reached the jejunum, they attain full maturity.

In America a disease closely similar to ankylostomiasis is produced by another but closely allied species called the *Necator americanus.*

Splenic Anæmia. This affection is badly defined, and more than one pathological condition has been included under the term. The anæmia usually met with is of the microcytic type. In addition to splenic enlargement there is in the majority of cases, cirrhosis of the liver, the condition being known as *hepato-lienal fibrosis.* The term ‘ Banti’s disease ’ is usually used as synonymous with the latter. The reduction in the red corpuscles is moderate, as a rule, but sometimes it advances and may become of marked degree. Reticulocytes are scanty and normoblasts are rare. The colour index is usually below unity, often distinctly so. But in a small proportion of cases with advancing anæmia, the index has been above unity, and even megaloblasts have been found. The leucocytes are generally much reduced in number, the count being often 2,000–3,000 per c.mm. or even less, and the fall is on the part of the polymorpho-nuclears. The platelets in some cases are about normal in number, in others distinctly decreased. The van den Bergh reaction is negative. The anæmia may be increased by hæmatemesis when there is portal congestion from cirrhosis of the liver.

The condition of the spleen, etc., is described later (p. 497). In the meantime it may be said that excision of the spleen is in many cases attended with marked improvement, especially when the disease is at an early stage. After splenectomy a blood crisis with numerous normoblasts and reticulocytes in the blood may occur (Fig. 300). There is also a rise in the number of platelets and it has been noted that in cases where the number has been normal originally, the great rise following operation may be accompanied by a tendency to thrombosis. Splenectomy is for this reason considered to be more successful when thrombocytopenia has been present. (Rosenthal.) The causation of the anæmia is not known, but the results of splenectomy suggests that the spleen contains an agent which is harmful to blood formation.

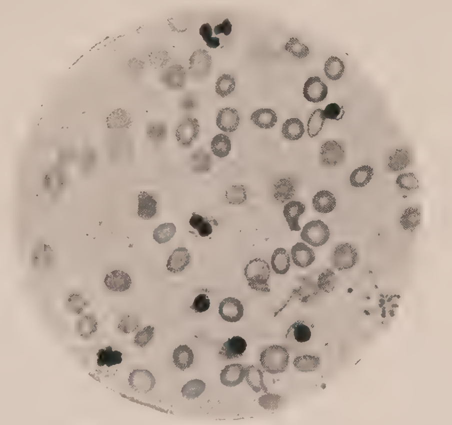

Fig. 300.—Blood in Splenic Anæmia, showing six Nucleated Red Corpuscles (Normoblasts).

The film represents a condition of blood crisis, which occurred after splenectomy. (Dr. Douglas Stevenson.) × 400.

Hæmolytic Anæmia

The chief types met with clinically of this form of anæmia are due to a defect in the erythrocytes in consequence of which they undergo more rapid dissolution. Acholuric jaundice and sickle-cell anæmia are notable examples; malarial anæmia is another. But, as has been stated, hæmolytic anæmia may be produced by extrinsic poisons or other agencies.

The Anæmia of Acholuric Jaundice. This is a chronic anæmia characterised by an abnormal state of the red corpuscles and increased hæmolysis. It is usually described as of two forms—(*a*) congenital, and (*b*) acquired.

In the *congenital* type, which is the commoner and better defined condition, the disease often affects more than one of the same family and is also hereditary. In some instances it has been traced through several generations; it is transmitted by either parent. Its existence is usually indicated first by a yellowish tint of the skin and conjunctivæ, this usually occurring in the earlier years of life though sometimes not till later. It is a chronic condition and may be attended with little disturbance of health, but exacerbations with increase of the anæmia and jaundice are apt to occur from time to time.

The *blood* shows a moderate diminution in the number of red corpuscles; the colour-index is about normal or even a little raised. The corpuscles appear smaller than normal, but are thicker and more of a globular form; their true size or 'mean corpuscular volume' is normal. A few normoblasts are often present; poikilocytes are scanty or absent. The leucocytes and platelets are little changed; the former tend, on the whole, to be rather diminished in number. A very important feature is the increased number of reticulocytes, these often reaching a percentage of 20–30 or even higher, and polychromatic erythrocytes are correspondingly numerous. This, of course, means that a large number of young corpuscles are entering the blood and also, as the count of the red cells may be little changed over a period, that the corpuscles are short-lived. Occasionally there are periods of more rapid destruction with fall in the red cell count, and these are followed by increase of reticulocytes and often of erythroblasts. Another important change is the increased fragility of the red corpuscles (p. 441), both the minimum and maximum resistance being lowered. This obtains both with regard to hypotonic salt solutions and other agents which produce lysis. It is a fact of interest that fragility of red cells may be found in the apparently healthy relatives of those suffering from the disease.

There is also *siderosis* of organs. The spleen shows marked enlargement though not so great as in some other conditions (p. 496); its weight usually does not exceed 3 lbs. It contains a large amount of blood, but the most important change is the accumulation of hæmosiderin which is stored in the reticulum cells of the pulp as well as in the endothelial cells of the sinuses. The sinuses are sometimes outlined owing to the large amount of pigment which they contain (Fig. 301). In addition, the connective tissue of the organ and the walls of the blood vessels may give a diffuse iron reaction. The amount of hæmosiderin in the spleen probably depends on the amount of blood destruction going on at the time. The liver usually contains a large amount of hæmosiderin, this being contained as in pernicious anæmia within both liver cells and Kupffer cells. There may be also some

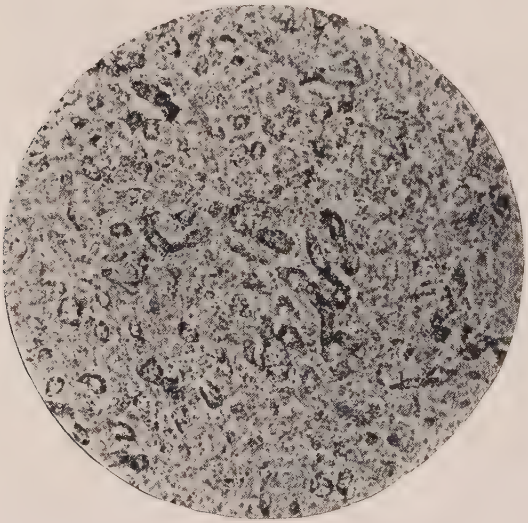

Fig. 301.—Section of enlarged Spleen in Acholuric Jaundice, stained to show deposits of Hæmosiderin.

Note that the hæmosiderin is specially abundant in the lining of the venous sinuses which are outlined by the darkly-stained granules. (D. F. C.) × 100.

accumulation of hæmosiderin in the kidneys, though their condition varies greatly in this respect.

Evidences of *increased hæmolysis* are present. There is a distinct increase of bilirubin in the blood and this gives an indirect van den Bergh reaction. To this is due the yellowish tint of the skin. The urine contains urobilin and urobilinogen but no bilirubin. The bile contains an excess of bilirubin, and the presence of pigment gall-stones has been observed in a large proportion of cases.

Increased hæmopoiesis is shown by a marked normoblastic reaction of the bone-marrow; the shafts of the long bones are filled with red marrow and there may be absorption of bone trabeculæ. There may also be myeloid transformation in the spleen. Another interesting fact is that in some cases extra-osseous nodules or even masses of myeloid tissue have been found under the pleuræ in the costovertebral angles in the thorax. It is not clear whether these represent areas of myeloid transformation or heterotopias which have occurred in development and then become hyperplastic as a result of the disease.

The essence of the disease is thus a congenital abnormality of the red corpuscles whereby they are more fragile and are destroyed more rapidly by the spleen. Excessive destruction and compensatory formation of corpuscles are going on. Removal of the spleen leads to disappearance of the abnormal hæmolysis almost at once. The van den Bergh reaction becomes negative, the number of red corpuscles gradually rises, whilst the percentage of reticulocytes diminishes. These favourable effects are often of a permanent character; the fragility of the red corpuscles is, however, not affected.

Cases of the so-called *acquired* type are a less definite class, the clinical and pathological features being less constant. Some occur in the course of other diseases, some apparently apart from them. It is possible that in some cases of the latter class we may merely have examples of the congenital type in which the effects of the inborn abnormality have become manifest at a later period of life. In certain instances, however, no hereditary or familial element can be traced. The disease is often of a severe character and anæmia becomes marked. Reticulocytes are numerous but the fragility of the erythrocytes may not be increased. It is hardly possible to say how the affection as a whole should be regarded.

Sickle-Cell Anæmia. This disease, which has been recognised in America within recent years, occurs in negroes and appears to be fairly common. It is characterised, as the name indicates, by the peculiar crescentic or sickle-like forms of the red corpuscles. These forms are scanty in fresh blood but they increase in number when the blood is kept in the fluid state, till after some hours a large proportion of the corpuscles may have assumed the characteristic shape. The abnormality depends on some inherent defect in the structure of the red corpuscles and not on any change in the blood serum. Thus, for example, the corpuscles undergo the same changes in normal serum, while normal corpuscles placed in the serum from a case of the disease maintain their normal form. The accompanying anæmia is usually slight or of moderate degree, although the number of red corpuscles may occasionally fall below 2,000,000 per c.mm. Other alterations such as poikilocytosis, polychromasia, the presence of erythroblasts, etc., are met with in varying degree. Reticulocytes are increased and may number 20 per cent or even more. There may be also phagocytosis of red corpuscles by non-granular cells. The colour index is about normal, but rather above unity in some of the cases. A certain degree of leucocytosis seems to be the rule and the number of polymorpho-nuclears is increased. The anæmia is of the hæmolytic type as is shown by increased bilirubin in the blood, urobilin in the urine and deposits of hæmosiderin in organs, especially in the liver. The disease thus presents a resemblance to the anæmia of acholuric jaundice; in both there is an increased hæmolysis owing to an inherent abnormality in the erythrocytes. There is, however, no increased fragility of the red cells in sickle-cell anæmia. The disease is hereditary and of the familial type, and Huck has found that it is transmitted according to the Mendelian law, the sickle-cell condition being a dominant. Nothing is known as to the etiology of the disease or of the nature of the essential abnormality in the erythrocytes. It may be added that a certain degree of the sickle-cell peculiarity has been noted in a small proportion of healthy negroes. The peculiarity is best found by keeping a sealed cover-glass preparation of fresh blood for some hours, as the deprivation of oxygen brings out the sickle form.

Other forms of hæmolytic anæmia need only be briefly referred to. In malaria and in Oroya fever the anæmia is produced by actual invasion of the erythrocytes by the respective parasites; the former is described below. Again the toxins of certain bacteria have hæmolytic action. Those of the *Streptococcus pyogens* and *Cl. welchii* are noteworthy examples. Lastly, there is a large group of chemical poisons which have a hæmolytic effect, such as arseninsalted hydrogen, toluylenediamine, saponin, potassium chlorate, etc., and some of these have been extensively used in experimental investigation. Some poisons have both a destructive effect on the red corpuscles and also on the bone marrow, leading to a certain amount of aplastic change in the latter. The number of reticulocytes in the circulating blood offers a valuable indication as to the compensatory regeneration which may be going on.

Aplastic Anæmia. This name may be conveniently applied when insufficiency or want of reaction of the bone-marrow is concerned in the production of the anæmia. There may be said to be two varieties of the condition: (*a*) In one, the abnormality is to be ascribed to some congenital or constitutional defect. (*b*) In the other, it is to be regarded as the effect of toxic action on a previously healthy marrow. The terms primary and secondary may be conveniently applied.

Of the *primary* variety, one type is met with in the early years of life and is characterised by a marked deficiency in the formation of all the elements produced by the marrow—erythrocytes, granular leucocytes and platelets. Reticulocytes are practically absent. There is no evidence of blood destruction and the colour index is not raised. Cases of this kind are rare. In a case of aplastic anæmia occurring in a child, which we observed, there was very little red marrow in the body, even the short bones being filled with a whitish fatty marrow. The red corpuscles fell to less than 1,000,000 per c.mm., no erythroblasts were present in the blood, the colour index was below unity, and there was a remarkable paucity both of polymorpho-nuclear leucocytes and platelets. Cases recorded by others have shown corresponding changes. A purpuric eruption often present is apparently to be related to the deficiency of platelets.

The condition of the marrow in such cases probably represents an inborn defect, but its true nature is unknown.

Another example of apparently primary aplasia is that met with in some cases of pernicious anæmia. It is a condition of rare occurrence. Instead of the usual hyperplasia of the marrow there may be an actual deficiency (p. 455). Here also it is probable that this represents a constitutional defect, though its causation is quite obscure.

There is also a *secondary* aplastic anæmia which may be produced in various ways. Aplasia may be due to damage to the marrow by chemical poisons such as benzol and its derivatives, lead, mercury, etc., or by X-rays or radium emanations. A remarkable example of this last is the anæmia which has been observed in America amongst girls working with luminous paint, which contains radium and mesothorium ; the condition apparently arises from pointing with the lips the brushes used. There is a severe anæmia, sometimes leading to a fatal result, and it is often associated with necrosis of bone. Sarcoma has developed in one or two instances (p. 265).

Myelopathic or Osteosclerotic Anœmia. These terms have been applied to an anæmia resulting from lesions of the bones involving the marrow. The condition is met with in secondary carcinomatosis of bones, in sclerotic conditions e.g. marble bone disease, and occasionally (rarely) in myeloma. The anæmia is characterised by the entrance into the blood of cells of both series, from the marrow rather than by its intensity. There may be a considerable number of erythroblasts, chiefly normoblasts and more primitive erythroblasts, though there may also be megaloblasts. Also a considerable number of reticulocytes are usually present. The leucocyte count is distinctly raised owing to increase of polymorpho-nuclears along with some myelocytes and intermediate cells. The condition has accordingly been called leuco-erythroblastic anæmia by Turnbull and Vaughan. In some cases there may be actually an increase of red marrow, for example, round cancer nodules, and the anæmic condition in these cannot be ascribed to a crowding out of hæmopoietic tissue by the lesions mentioned. In other cases the sclerotic changes in bones may lead directly to marrow deficiency. There may also be formation of myeloid tissue in liver, spleen, etc.

THE ANÆMIAS OF INFANCY AND CHILDHOOD

The following is a short account of the chief varieties, the two first being those of most frequent occurrence in this country.

Nutritional anæmias. These may be due to deficiency of iron in the mother's diet during pregnancy or insufficient storage of iron on the part of the fœtus, or after birth to inadequate amounts of iron in the milk fed to the infant. The anæmia is of microcytic type with low hæmoglobin and low colour index, and scanty or no nucleated red cells. A similar type of anæmia is present in infantile scurvy (p. 839). The anæmia associated with cœliac disease is usually of the microcytic type though sometimes megalocytic.

Hæmolytic anæmias (erythroblastosis of new-born). These anæmias occur shortly after birth, are usually fatal, and are often associated with jaundice or dropsy. Frequently, they are of familial nature. The colour index is usually above unity, and many erythroblasts and reticulocytes are present. An important example is *icterus gravis neonatorum.* In it the liver in some cases is deeply bile-stained and shows evidence of necrosis of liver cells, and throughout its substance are very numerous areas of erythropoiesis. The spleen is enlarged, congested, and foci of erythropoiesis are found in it also. Much hæmosiderin pigment is found in both organs. The marrow of the long bones is usually deficient in amount, and erythroblasts are scanty. The tissues of the central nervous system are sometimes bile-stained, particularly the basal nuclei (Kernicterus). Another example of the same group is *congenital hydrops fœtalis*, where there is widespread œdema.

In later childhood both secondary anæmias and primary hæmolytic anæmias are met with. In the rare type described by Lederer, there is a sudden onset of a profound hæmolytic anæmia, often associated with acute gastro-intestinal symptoms, suggesting that this disease may be infective in origin.

Von Jaksch's Anæmia.—This affection, which is known also as *anœmia pseudo-leukœmica infantum,* is somewhat badly defined. It is met with in children usually in the first three years of life, and is characterised by anæmia, increased number of leucocytes and splenic enlargement. The anæmia is usually of the hæmolytic type, with a colour index less than unity, but some cases have been described in which there has been a high colour index with the presence of megaloblasts, etc. The number of leucocytes is raised, often being 20,000-25,000 per c.mm. or even more, and a feature is the great variety in the characters of the leucocytes. Increase affects all varieties, and ill-defined types of cells may be present ; sometimes lymphocytes and sometimes granular cells may be the more numerous. Myelocytes also may be present and there may be numerous normoblasts ; occasionally also megaloblasts. The affection is often a very chronic one, the condition of the blood remaining little changed for a long time ; and recovery appears to be not infrequent. Some consider that von Jaksch's anæmia is a distinct disease, but by others it is regarded as a condition which may be produced secondarily by rickets, syphilis, gastro-intestinal disease, etc. A definite statement on the question cannot be made. It is noteworthy that this type of anæmia is much less common than formerly.

A form of anæmia with splenomegaly in the child has recently been described under the name of *erythroblastic anœmia* (Cooley). It has been observed in children under two years of age from Mediterranean countries and has a familial character. It is essentially a hæmolytic anæmia, microcytic in type and often severe. The blood gives an indirect van den Bergh reaction. There is a large number of erythroblasts in the blood with greatly increased number of reticulocytes ; usually also leucocytosis with varieties in the types of cells. A marked accumulation of hæmosiderin is present in organs and is widespread, occurring in pancreas, stomach wall, etc. The bone-marrow is actively hyperplastic and myeloid metaplasia is present in organs. The bones also show structural changes, one of the most striking being a great thickening of the calvarium with much increase of the diploë. The cause of the disease is unknown. It still remains to be determined what is the relation of this condition to Von Jaksch's anæmia.

Malarial Fever and Anæmia. In connection with the subject of malarial anæmia it will be necessary to give a brief account of the varieties of malarial fever and their causation. It is now well established that there are three types of malarial fever caused by three different parasites. These are (*a*) the tertian caused by the *Hæmamœba vivax* or *Plasmodium vivax,* (*b*) the quartan caused by the *Hæmamœba malariæ* or *Plasmodium malariæ,* and (*c*) the sub-tertian or malignant malaria caused by the *Hæmomenas præcox* or *Plasmodium falciparum.* These parasites belong to the hæmosporidia, a sub-class of the sporozoa. The two first are closely allied, being of the same genus, and the gametocytes or sexual cells are of spherical form ; the third is of another genus and the gametocytes are crescentic in shape. Each parasite passes through two cycles of development—an asexual one or *schizogony* in the human subject, and a sexual one or *sporogony* in the mosquito. In the former cycle, the gametocytes are formed, but undergo no further development, whilst in the latter conjugation of the gametes formed from the gametocytes takes place and further changes follow. A number of species of mosquito have been found to be capable of carrying infection, but these all belong to the genus *Anopheles.* The onset of a febrile attack of malaria coincides with the setting free of a new brood of young parasites by the asexual division of the adult forms, and the period of the fever depends on the time taken for the full development from the young to the adult form. In quartan fever this period is seventy-two hours and the fever occurs every third day ; in tertian fever the period is forty-eight hours and the fever occurs on alternate days ; in the sub-tertian the period is probably the same, but multiple infection is common and the attacks of fever vary, sometimes being daily. Multiple infection occurs when parasites are introduced by mosquitoes on more than one occasion, so that the parasites of different sets may be at different stages of development. Sometimes also mixed infection occurs, e.g. by the tertian and sub-tertian parasites. The stages of development of the parasites may now be described more in detail (*vide* Fig. 302).[1]

Cycle of Development in the Human Subject. If the blood be examined at the onset of a febrile attack, numerous young parasites derived from the preceding generation (*vide infra*) may be seen within the red corpuscles. They are of small size, measuring about 2 μ in diameter, and consist of a protoplasmic body with a nuclear mass of chromatin which is coloured red by Leishman's or other stain of similar nature. They vary in form, but not infrequently are ring-shaped with a thickening at one side where the nucleus is present. These intra-corpuscular forms are known as *trophozoites* and they grow at the expense of the red corpuscles, destroying their substance. They assume various shapes as they enlarge, and fine granules of pigment accumulate in their substance. The protoplasm of the trophozoites is coloured a faint blue by the stain mentioned, and the small mass of nuclear chromatin is often surrounded by an unstained area or vacuole. When they become mature. that is, at the end of the period mentioned above, some of them undergo division or schizogomy, whilst others are destroyed and disappear. In the cells in process of division, known as *schizonts*, the nuclear chromatin takes up a central position and divides into a number of minute fragments or young nuclei ; the protoplasm then becomes segmented and the result is that a number of somewhat oval bodies, each of which contains a minute mass of nuclear chromatin, are formed. These segments or young cells, which are called *merozoites*, are set free by the bursting of the envelope of the red corpuscle. Some of them invade fresh corpuscles, and thus the cycle is completed.

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[1] For a detailed account of malaria and other protozoal infections, see *Protozoology*, by C. M. Wenyon, London, 1926.

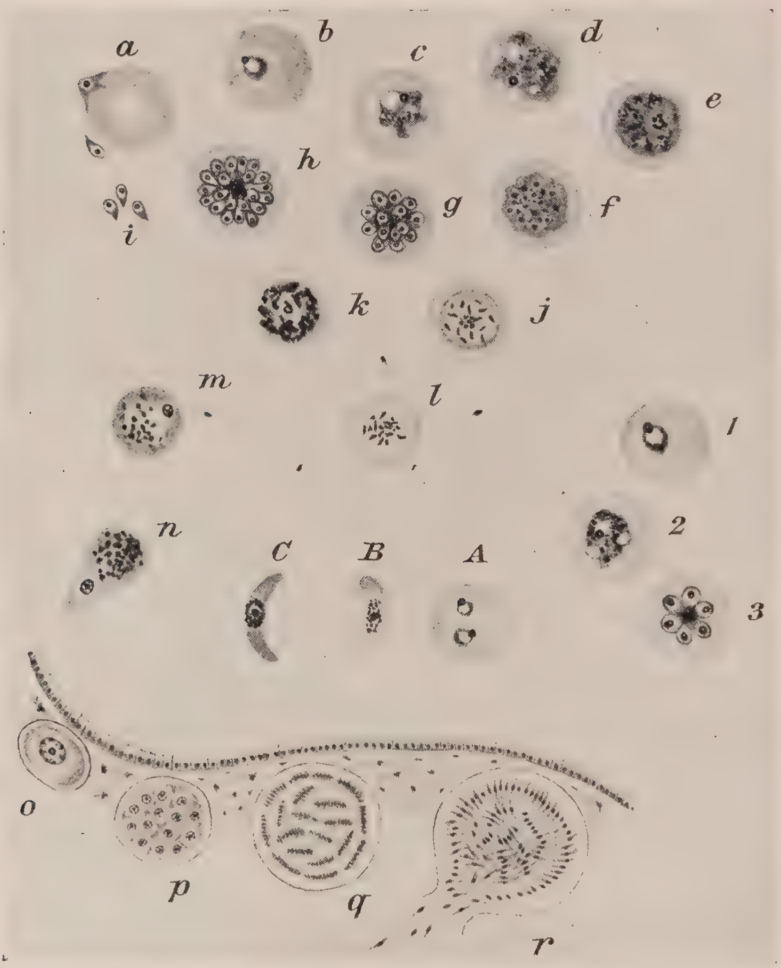

Fig. 302.—Stages of Malarial Parasites. (Rd. M.)

a–r, Parasite of tertian malaria.—*a*, merozoite entering red corpuscle ; *b*, young trophozoite or 'ringed-form' within corpuscle ; *c*, young pigmented trophozoite ; *d*, large pigmented trophozoite ; *e*, mature schizont ; *f*, commencing segmentation of schizont ; *g*, merozoites forming from schizont ; *h*, cluster of merozoites around mass of pigment ; *i*, free merozoites passing to fresh corpuscles ; *j*, male sporont (gametocyte) ; *k*, female sporont ; *l*, male sporont forming microgametes ; *m*, microgamete passing to macrogamete ; *n*, zygote or oökinete ; *o*, sporocyst in wall of stomach of mosquito ; *p*, sporocyst with formation of sporoblasts ; *q*, sporozoites forming from sporoblasts ; *r*, rupture of sporocyst and setting free of sporozoites.

1–3, Parasite of quartan malaria.—1, young trophozoite ; 2, pigmented trophozoite ; 3, segmenting schizont—daisy-form.

A—C, Parasite of sub-tertian or malignant malaria.—*A*, trophozoite, small ringed-form ; *B*, male sporont or 'crescent' ; *C*, female sporont or 'crescent.'

Many of them, however, become destroyed by phagocytic action or in other ways. None of the pigment formed by a trophozoite passes into the merozoites ; it is set free on the separation of the latter, and is carried by leucocytes to various organs, especially to the spleen and liver.

The asexual cycle is essentially the same in all the parasites, but some features may be mentioned which aid in distinguishing them. The quartan and tertian parasites resemble each other, and the schizont of each occupies nearly the whole of the invaded red corpuscle. The *quartan* parasite has coarser pigment, the invaded corpuscle is unaltered in appearance, and the schizont divides into 6–12 merozoites which are arranged in a radial manner, giving a daisy-head appearance. The *tertian* parasite has finer pigment particles, the invaded red corpuscles are often paler and swollen, and the merozoites are 15–20 in number and arranged in a cluster or rosette. In tertian infections, some of the red corpuscles often contain minute granules which are stained red by Leishman's stain ; they are known as Schüffner's dots. The *sub-tertian* parasite is of smaller size than the other two, and the adult trophozoites occupy only a part of the corpuscle. The invaded corpuscles are sometimes pale, sometimes rather shrivelled and darker in tint. Schizogony occurs chiefly in the blood of the internal organs, and the schizonts, which are of small size, are not often seen in the peripheral blood ; the merozoites usually number 8–20. This form of fever is most readily recognised, however, by the presence of the crescentic gametocytes, which are quite characteristic.

The *gametocytes* are the sexual cells or sporonts which are formed from some of the larger trophozoites, and, as stated above, they do not take part in schizogony or undergo further development in the human body. In tertian and quartan malaria the gametocytes are spherical in form. The female forms or *macrogametocytes* are the larger, and measure up to 16 μ in diameter ; their protoplasm stains somewhat deeply with methylene blue and contains relatively coarse granules of pigment, whilst the nucleus is often at the side. The male gametocytes or *microgametocytes* have a protoplasm which stains less deeply and contains finer granules of pigment, and the nucleus is usually central. In sub-tertian malaria, the gametocytes have a characteristic crescentic form, and the outline of the invaded red corpuscle is often indicated by a fine curved line joining the extremities. The macrogametocytes, which measure 9 μ in length, are distinctly crescentic with pointed ends ; the protoplasm again stains deeply, and several granules of dark pigment are concentrated around the nuclear chromatin, which is central in position. The microgametocytes are rather smaller and are more sausage-shaped. The protoplasm stains less deeply, the pigment is finer and more scattered and the nuclear chromatin also is less concentrated. It is to be noted that the gametocytes are not influenced by quinine, as the trophozoites are, and they may persist long after the febrile attacks have disappeared. By means of them the infection is maintained, and it is believed that the macrogametocytes may, without the occurrence of conjugation, give rise under certain circumstances to merozoites.

Cycle in the Mosquito. When the blood containing the parasites enters the stomach of the mosquito, there occur further changes which commence with maturation of the gametocytes or sporonts followed by conjugation. Each macrogametocyte gives off small masses of chromatin from the nucleus and becomes a ripe female cell or *macrogamete.* The microgametocyte also gives off chromidia and the cell then becomes divided into 4–6 flagellum-like structures which are the *microgametes* ; each of these has a minute rod of chromatin as a nucleus. The microgametes then become free as actively moving cells in the surrounding fluid. Conjugation occurs by the entrance of a microgamete into a macrogamete and thus fertilisation occurs, the result being a *zygote.* In the case of the sub-tertian parasite the crescentic gametocytes become first oval and then spherical, and the subsequent changes are of a nature similar to those described. The fertilised cell or zygote becomes a motile *oökinete,* which penetrates the wall of the stomach of the mosquito and then becomes encysted, the result being a *sporocyst.* Within the sporocyst the cell divides and gives rise to a number of cells or *sporoblasts,* and each of these becomes in turn segmented into a number of radially arranged filiform cells or *sporozoites.* The sporocyst, which is enlarged during these changes, then ruptures, and the sporozoites being set free in the body cavity, pass to the cells of the salivary gland. They are then readily introduced into the human tissues when the insect bites. A period of about twelve days elapses after the ingestion of the blood by the insect till the appearance of the sporozoites in the salivary gland.

Malarial Anœmia. With each attack of pyrexia in malarial infection a large number of red corpuscles are destroyed by the actual invasion of the parasites, and the dark brown pigment formed from the hæmoglobin is deposited in the spleen, liver, and other organs. It is accordingly not surprising that when the disease has lasted for some time anæmia should be present, and that in a proportion of chronic cases it should become very marked. The occurrence of blackwater fever, due to intravascular hæmolysis, will of course greatly intensify the anæmia. Malarial anæmia is generally of the hypochromic type, though the colour index is not much reduced. At an early stage, the blood destruction leads to a response indicated by an increased number of reticulocytes, but in chronic cases deficient formation of red cells may be present. A few normoblasts may sometimes be found. The leucocyte count is usually somewhat reduced, though it varies, and a noteworthy feature is the increase of the mononuclear leucocytes, the percentage of which often reaches 15–20, or even more. Some of these may contain malarial pigment. Cases of severe malarial anæmia are sometimes met with, in which the anæmia becomes of the megalocytic type. The reason for this is not fully understood, but in some cases at least the cause is the absence of the extrinsic factor.

Blackwater Fever. In blackwater fever there occurs a lysis of red corpuscles in the circulating blood with resulting hæmoglobinæmia ; thus hæmoglobinuria and methæmoglobinuria follow. This imparts to the urine a dark brown or almost black colour, hence the name. The hæmoglobinuria is accompaned by pyrexia, and other symptoms such as vomiting, convulsions, and coma, often followed by a fatal result ; sometimes there is suppression of urine before death. In the great majority of cases blackwater fever occurs in patients who are suffering or have suffered from malaria, but its exact causation is still a matter of dispute, and it is believed by some that a previous attack has a ‘ sensitising ’ effect. Others hold that it is the result of administration of quinine to a malarial patient with special susceptibility to the drug. It is generally recognised that in some cases quinine may precipitate the attack, but, on the other hand, the disease may occur when no quinine has been given. Christophers and Bentley found that in the blood in blackwater fever there is a substance of the nature of an immune-body (autolysin) which, in association with complement, leads to solution of the red corpuscles, this lysin being apparently developed as the result of the blood destruction in malaria. This has, however, not been established. Fairley and Bromfield have recently shown that the lysis of the erythrocytes in the circulation is attended by the formation of a special pigment to which they have given the name pseudo-methæmoglobin. This pigment does not function as an oxygen carrier and is not excreted in the urine to appreciable extent ; in this way iron is conserved in the body. These results are highly interesting, but the causation of the hæmolysis is not cleared up.

HYPERPLASTIC DISEASES

Leukæmia.[1] In this disease there is a remarkable increase of the leucocytes in the blood, which does not correspond in character with that of a reactive leucocytosis. There are two main varieties of leukæmia : one in which the cells in excess are of the myeloid series—**myeloid leukæmia** ; and another in which the cells are of the lymphoid series—**lymphatic leukæmia** or **lymphocythæmia.** There occurs also a hyperplasia in varying degree of the leucocyte-forming tissues ; and leucocytic infiltrations of various organs are common, especially in the lymphatic form. The disease is usually chronic, lasting sometimes a year or two, but there are cases which run a comparatively rapid course ; and these *chronic* and *acute* types occur in both the myeloid and lymphatic forms. Along with the leucocyte increase in the blood there is a varying amount of anæmia, which is more marked and advances more rapidly in the acuter cases. Recently there has been recognised a third type of leukæmia in which the monocytes are in excess—**monocytic leukæmia.** It is of relatively rare occurrence.

In all the forms of leukæmia the changes in the blood are to be regarded as merely secondary to the hyperplastic changes in the leucocyte-forming tissues. Sometimes cases are met with in which these latter changes have occurred without there being an increase of leucocytes in the blood, and the term ‘ aleukæmic leukæmia ’ is then usually applied. An aleukæmic stage will occur in every case of leukæmia but it is seldom observed except in the lymphatic form. One meets sometimes with a case of enlargement of lymphatic glands in which at first the blood leucocytes are normal, while at a later period there is a relative increase of lymphocytes with a normal leucocyte count, and later still a great total increase of lymphocytes may appear.

The Blood. In *myeloid leukæmia* the number of leucocytes may be enormously increased, and in consequence of this and the anæmia often present, the blood may be paler and rather more opaque-looking than the normal. A count of 300,000 per c.mm. is not uncommon, but considerably higher figures may be met with. The main increase is on the part of the finely granular neutrophile cells, and these comprise both the ordinary polymorpho-nuclear leucocytes and their corresponding myelocytes, along with intermediate forms (Fig. 303). The proportion of the two types of cells varies much ; the former are usually distinctly more numerous, but sometimes the myelocytes may approach or even exceed them in number, especially in the less chronic cases. Other granular cells, eosinophiles and basophiles may occur in considerable numbers, but vary much in different cases. Sometimes eosinophiles are numerous, sometimes basophiles, and sometimes neither; both occur as myelocytes and as the ordinary polymorpho-nuclear forms. In a few cases the chief increase has been on the part of the eosinophiles. In addition to the ordinary myelocytes with neutrophile reaction, there are earlier stages, i.e. similar cells with fine basophile granules or granules giving intermediate reaction, and also still younger cells, without granules—*myeloblasts* (p. 79). These last are especially numerous in the more acute cases, and sometimes they are almost the only cells present; they indicate that

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[1] For a full account see *Leukæmia and Allied Diseases*, by Claude E. Forkner, New York, 1938.

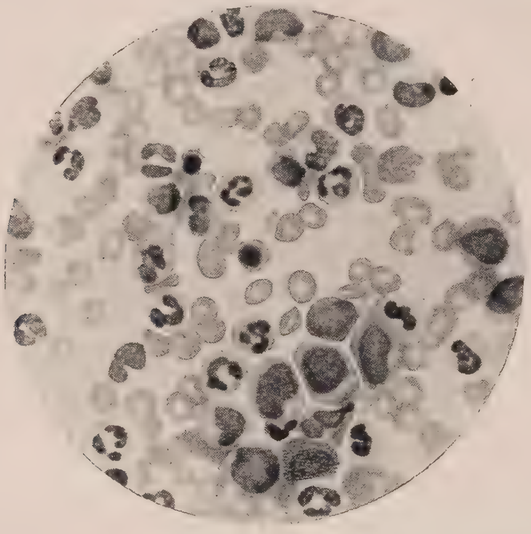

Fig. 303.—General view of Chronic Blood in Myeloid Leukæmia, showing Myelocytes, Polymorpho-nuclear Leucocytes and intermediate forms; two Erythroblasts are seen near centre of field. × 500.

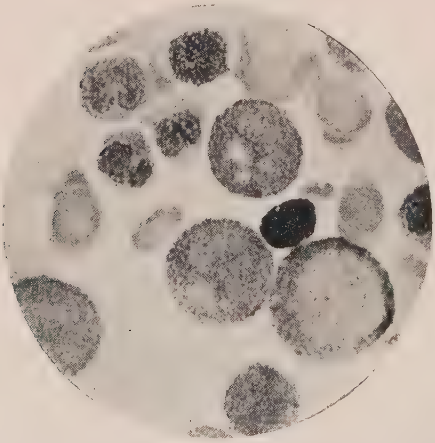

Fig. 304.—Blood in Chronic Myeloid Leukæmia, showing finely granular Myelocytes and Polymorpho-nuclear Leucocytes; the dark cell near the centre is a basophile. (Prof. E. M. Dunlop.) × 1,000.

younger and less differentiated cells are entering the blood from the marrow (Fig. 305). Such cells come to resemble the large lymphoblasts seen in acute lymphatic leukæmia, and in some cases it may be difficult to draw the distinction. A positive oxydase reaction indicates that the cells in question are of the myeloid series, as the reaction is not given by cells of the lymphocyte series; but the absence of reaction is not conclusive, as young myeloblasts may not give the reaction (*vide* p. 443). Erythroblasts also are present; they are chiefly normoblasts, and may occur in large numbers, being sometimes more numerous than in any other disease.

In the more chronic cases of myeloid leukæmia there is usually a moderate reduction in the number of the red corpuscles, with some reduction in the colour index. In acute cases, however, there is often a rapidly advancing anæmia with tendency to the occurrence of hæmorrhages. The blood platelets are usually increased in chronic myeloid leukæmia and may be very numerous. In the acute form, on the other hand, they are usually much reduced.

It is thus seen that in myeloid leukæmia there is an overflow, as it were, of the cells of the marrow into the blood, and the cells present represent different stages in the formation of the granular leucocytes. Further, the more acute a case is the more do the younger undifferentiated cells or myeloblasts predominate. It also may be added, that sometimes under treatment the number of leucocytes may fall greatly and may reach the normal level; but even then myelocytes are still present, as a rule.

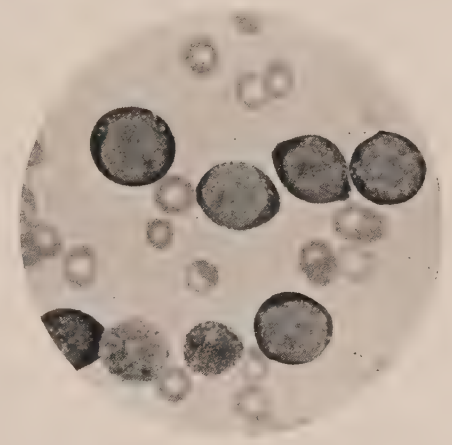

Fig. 305.—Blood in Acute Myeloid Leukæmia showing large mononuclear Cells which are Myeloblasts. (J. S. D.) × 1,000.

In *lymphatic leukæmia* the blood picture is much simpler and presents a marked contrast to that described. The increase is on the part of the lymphocytes, and these cells often number more than 95 per cent. of the cells present. In the chronic cases nearly all may be small lymphocytes (Fig. 306), or there may be admixture of large forms; whilst in many acute cases nearly all may be of the large variety, or lymphoblasts, which may show aberrant characters. The other cells are not increased and are often actually diminished in number. The number of leucocytes in the chronic lymphatic type may reach as high a figure as in the myeloid type, but is usually less raised. In acute cases the number may be little above normal: the chief feature being the large proportion of lymphoblasts. Anæmia tends to be more marked than in myeloid leukæmia; it is of the secondary type with the usual accompanying changes. Erythroblasts are in general scanty and may be absent. As a contrast to what occurs in the myeloid form the platelets are usually scanty and may be almost absent. This change and also the fall in number of the erythrocytes are apparently due to the replacement of the marrow tissue by lymphocytes.

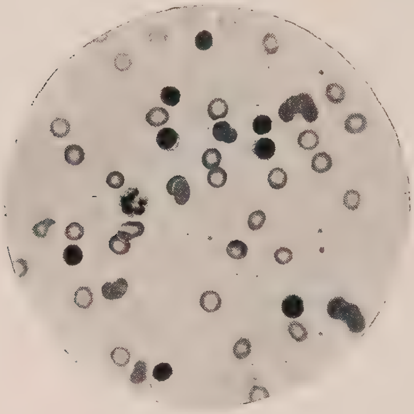

FIG. 306.—Film of Blood in Chronic Lymphatic Leukæmia, showing increase of small Lymphocytes.

The red corpuscles are scanty and show 'ring staining' owing to deficiency of hæmoglobin. × 400.

It will be seen from the above that in the acute cases, both myeloid and lymphatic, the number of leucocytes may be little raised, while the cells are chiefly of primitive type. There is often a tendency to hæmorrhages and also to inflammatory conditions about the mouth. Intermediate types between the acute and chronic occur, but as a rule cases fall readily into one or other of the two main classes.

The Bone Marrow. In both types the fatty marrow is replaced by a cellular marrow of pale colour, and not infrequently there is considerable absorption of bone trabeculæ, so that it is easy to cut out large portions (Fig. 308). The colour is usually pinkish-grey with redder streaks and patches, and sometimes it has a slightly greenish tint; in the myeloid type autolytic softening may be present *post mortem*, so that the marrow may have an almost puriform appearance. The condition in the two varieties is found, on microscopic examination, to correspond with the blood picture. In the myeloid type there

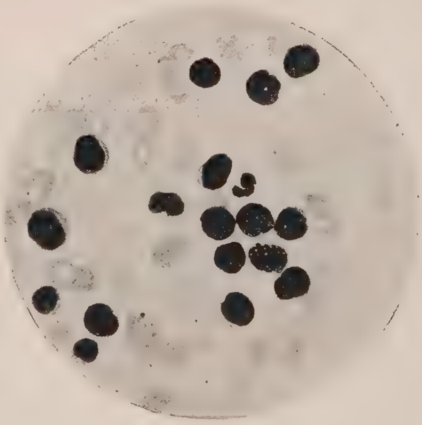

FIG. 307.—Blood in Acute Lymphatic Leukæmia, showing increase of larger Lymphocytes. (E. M. D.) × 400.

is an enormous hyperplasia of the cells of the marrow, the finely granular myelocytes and myeloblasts, however, markedly preponderating, the latter being the chief cells in acute cases. Erythroblasts are still present, but are relatively reduced in number.

In the bone-marrow and various tissues rich in leucocytes there are often to be found small crystals known as Charcot's crystals; they are elongated octahedra of about 10 μ in length. Such crystals are found, moreover, along with eosinophile leucocytes in the bronchial tubes in asthma, and there is considerable evidence that they are derived from these cells. They do not occur in the lymphatic form of leukæmia.

In the lymphatic type, the cells proper to the marrow may have almost disappeared and been replaced by masses of lymphocytes, between which run blood vessels with thin and badly defined walls. Erythroblasts are very scanty and it may be difficult to find any. The marrow tissue proper is thus practically destroyed by the lymphocytic invasion, and in this way the anæmia is brought about.

The various marrow changes described are sometimes associated with a dull pain in the bones, especially in the sternum.

The Spleen. Great enlargement of the spleen is a common feature in leukæmia. It is commoner in the myeloid type, where the weight of the organ may reach six pounds, or even more, but occasionally in chronic lymphatic leukæmia almost as great a size may be met with. There is no doubt that the size of the organ depends mainly on the duration of the disease, being greatest in the chronic cases. In the more acute types, the enlargement is only moderate, or may even be slight. A large spleen in leukæmia has usually a moderately firm consistence and, on section, shows a fairly uniform or somewhat mottled pale red surface, in which the Malpighian bodies, as a rule, cannot be distinguished. Infarctions are not infrequently present and may be of large size. They are of the anæmic variety and are probably the result of leucocyte thrombi. In the more acute cases, the organ is of normal or even subnormal consistence. The essential histological change in all cases may be said to consist in a packing of the pulp with leucocytes corresponding in character with those in

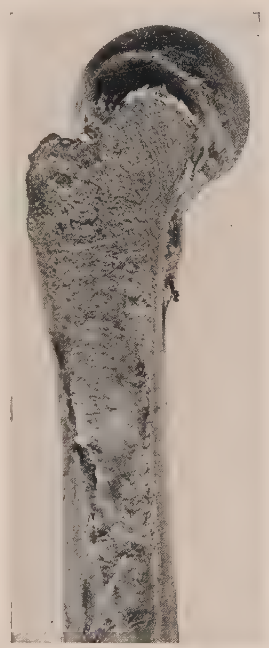

FIG. 308.—Section of Femur in Leukæmia.

The fatty marrow is replaced by a pale cellular tissue and there is also absorption of bone.

the blood. Thus, in the myeloid type the pulp is occupied chiefly by myeloblasts, myelocytes and granular leucocytes, whereas in the lymphatic form the cells are lymphocytes. It seems quite likely that enlargement of the spleen represents an attempt on the part of the organ to remove the cells in excess from the blood. In chronic cases a certain amount of thickening of the stroma follows. The Malpighian bodies usually take no part in the change and are of small size; they appear scanty owing to their being separated by the enlarged pulp. Sometimes a considerable amount of hæmosiderin is present in the pulp of the organ.

Lymphatic Glands. In the myeloid type, the glands may be practically unaltered to the naked eye, or some may be slightly enlarged. On microscopic examination, it is common to find accumulation of myeloid cells in the cortical sinuses extending into the peripheral parts of the lymphoid tissue the appearance being as if the cells had been carried to the glands by the lymphatics. Areas of similar cells may be scattered in the substance of the glands possibly as the result of myeloid transformation *in situ.*

In the lymphatic form there is usually marked enlargement of the lymphatic glands. In chronic cases this enlargement may affect many groups and reach a high degree, while in the more acute cases the enlargement is often localised to a particular region, and is less marked or may be slight. The glands have a cellular character and usually a greyish or pinkish-grey appearance, although occasionally hæmorrhages are present, especially in the more acute cases. The enlargement is due to an overrunning of the whole gland substance with lymphocytes similar to those in excess in the blood. The normal architecture of the glands is lost, and they have a uniform cellular character. There is little or no tendency to secondary fibrotic change even in very chronic cases.

In monocytic leukæmia, also, there occurs enlargement of lymphatic glands, though this may not be very marked. The cervical glands are those most commonly affected.

Changes in other Organs. These are chiefly of the nature of infiltrations of cells corresponding to those in the blood, and are especially met with in lymphatic leukæmia. Such infiltrations may be general and produce uniform enlargement of organs with pallor, or, on the other hand, they may give rise to irregular pale areas, or sometimes even to rounded tumour-like masses. A periportal infiltration of lymphocytes in the liver, with encroachment on the parenchyma, is common in lymphatic leukæmia (Fig. 309), and a similar condition is occasionally present in the kidneys, which may become greatly enlarged as a result; but the characters and distribution of such infiltrations vary greatly in different cases, and practically any organ in the body may be affected. In the myeloid type, collections of myelocytes, etc., are occasionally met with in the portal tracts of the liver and around capillaries in various organs.

In leukæmias generally, especially when there is marked anæmia, fatty degeneration and capillary hæmorrhages are of common occurrence in various organs, on serous surfaces, etc. In the brain, hæmorrhage of considerable size is occasionally met with, and is apparently the result of blocking of the vessels with leucocyte thrombi. Such hæmorrhage is often in multiple foci and irregularly distributed in the brain substance.

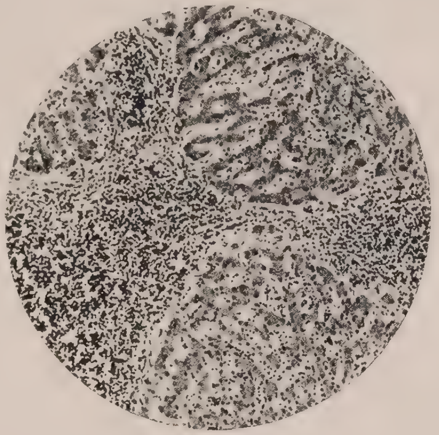

FIG. 309.—Section of Liver in Lymphatic Leukæmia, showing Infiltration of Lymphocytes around the portal Tracts. × 60.

Chemical Changes. In leukæmia, the amount of uric acid in the blood and in the urine is usually increased, and in the spleen there has been found an increase of uric acid and xanthine bases. These substances are derived mainly from nucleic acid, and their increase is no doubt due to the excessive breaking down of leucocytes which occurs in the disease. Bence-Jones protein is often present in the urine as in other conditions affecting the bone-marrow.

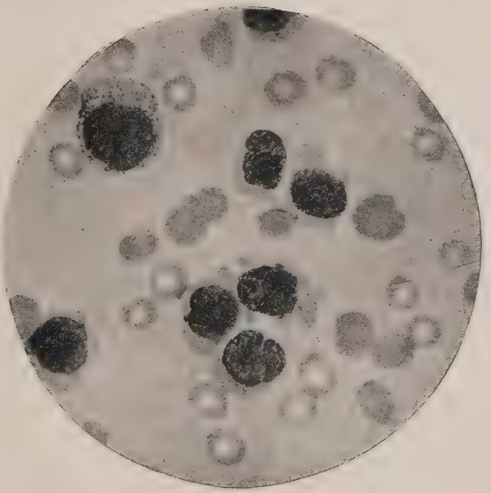

FIG. 310.—Blood in monocytic leukæmia. Note the characters of the nuclei and the pseudopodia. (D. F. C.) × 1000.

MONOCYTIC LEUKÆMIA. This has recently been recognised as a distinct variety; it is very rare but already a considerable number of cases have been recorded. It is relatively acute and is attended with inflammatory conditions of mouth and fauces, irregular pyrexia, advancing anæmia, petechiæ, bleedings from the mucous surfaces, etc. The leucocyte count is usually not very high but occasionally it is rather over 250,000 per c.mm. The percentage of monocytes may be 70 or higher and these cells give the characteristic segregation granules on supravital staining with neutral red. In addition to ordinary monocytes there are also larger cells of more primitive type, the cytoplasm of which often shows a projection of pseudopodia (Fig. 310). These larger cells have often been found to be oxydase-negative. Extensive leukæmic infiltrations leading to enlargement are found in various organs, lymph nodes, spleen, liver, etc., these being affected in varying degree as in other forms of leukæmia. In accordance with the view as to the origin of monocytes from the reticulo-endothelial system, the disease has been named a reticulo-endotheliosis. It is advisable that the neutral red staining should be carried out in leukæmia when the type is obscure; it is possible that monocytic leukæmia is commoner than has been supposed.

Chloroma. The term is applied to a greenish cellular tumour which is associated with acute leukæmia. The growth, which is often multiple, starts usually under the periosteum of the bones of the head, occasionally projecting into the orbit or cranial cavity, and afterwards may appear in other parts. The tissue of the growth has a distinct greenish colour which disappears on exposure to the air; the nature and significance of the pigment are unknown. As has been said, a leukæmic condition of the blood is present, and both myeloblastic and lymphoblastic cases have been described, but the evidence is that most are of the former type. The leucocyte count may not be much raised. The cells of the growths correspond in character with those in the blood, and the condition is of interest as suggesting an intermediate stage between leukæmia and ordinary tumour growth.

PATHOLOGY OF LEUKÆMIA. The cause of leukæmia is unknown; no parasite has been found. The facts known with regard to the disease indicate rather that it is a neoplastic process, corresponding to tumour growth. Acute cases are often attended by pyrexia, inflammatory change in the fauces, a tendency to hæmorrhage, etc., and the general features rather resemble those of an infective condition, but such symptoms may be really due to secondary bacterial infection. This will be apt to occur seeing that in acute cases the number of polymorpho-nuclears is much reduced; in fact a condition of agranulocytosis may be present.

The resemblance between leukæmia and malignant neoplasms is very striking. Leukæmia occurs in the lower animals and, among mammals, has been studied especially in mice and guinea-pigs. The disease can readily be transmitted from one animal to another of the same species, but only by means of the cells, not by any filterable agent. In mice it is a comparatively frequent disease, the lymphatic type being more common than the myeloid and often associated with lymphomatous tumours. A hereditary element seems to be involved, and an interesting fact is that lymphatic leukæmia becomes more frequent in mice treated with carcinogenic agents for other purposes. In fowls too leukæmia is comparatively common, different forms occurring, and it has been shown by Ellerman and others that it is transmissible to other fowls by a cell-free filtrate. In this respect there is a striking analogy to the filterable tumours of birds. Then again we have the fact that in leukæmia just as in tumours the more anaplastic or undifferentiated the cell is, the more rapid is the course of the disease. If all these facts are considered the conclusion is justifiable that leukæmia is just an example of neoplasia, and its features are due to the characters of the cells concerned and the absence of stroma formation.

Splenomegalic Polycythæmia or Erythræmia. In this condition there is, as has been stated, a marked increase in the number of red corpuscles per c.mm., and, as the colour index is only a little reduced, there is also a marked increase in the percentage of hæmoglobin. Further, the total quantity of the blood is considerably increased, that is, there is a true plethora, so that the increase of red corpuscles is greater than is indicated by the hæmocytometer count. The red corpuscles tend to be somewhat diminished in size ; some polychromatophile corpuscles and normoblasts are occasionally to be found in films. The leucocytes show little change, except a proportionate increase of polymorpho-nuclears observed in some cases. The enlargement of the spleen, which may reach a considerable degree, appears to represent an attempt to deal with the excessive amount of blood. The viscosity of the blood is increased, and accordingly also the frictional resistance ; and thus to maintain the circulation the left ventricle of the heart undergoes a certain amount of hypertrophy. The blood pressure becomes raised and ultimately arteriosclerosis may develop. The disease, as such, is usually met with in middle adult life, but no doubt it originates at an earlier period. The patient has commonly a florid appearance, and there is a tendency to cyanosis, especially on exposure to cold. The marrow in the shafts of the long bones is, as a rule, changed into red marrow of erythroblastic type, and this fact, along with the occasional presence of erythroblasts in the circulation, shows that there is an abnormally great production of erythrocytes. There is no evidence that this is of secondary or compensatory nature, or the result of some defect in the functional capacity of the red corpuscles. It has been supposed to be of neoplastic nature, analogous to the increase of leucocytes in leukæmia, and some such hypothesis must meantime be accepted.

HÆMORRHAGIC DISEASES

Under this heading we have grouped together a number of conditions—hæmophilia, purpura and scurvy—which are quite different in their etiology, but which have the common feature of a liability to the occurrence of hæmorrhages into the tissues and from mucous membranes. We have added also a short account of paroxysmal hæmoglobinuria.

The hæmorrhagic feature may be present also in some of the diseases already described, notably in acute leukæmia.

Hæmophilia. This affection is characterised by a congenital deficiency in the coagulating power of the blood. From any trifling wound there is persistent bleeding, while a larger one, such as that caused by the extraction of a tooth, has been known to lead to a fatal result. Effusions of blood and serum in varying proportion occur into the joints and into the subcutaneous tissues, giving rise to 'hæmatomata,' and this may happen either 'spontaneously' or as the result of slight injuries. When effusions take place into the joints, absorption of the blood is slow and often imperfect; fibrous adhesions leading to partial ankylosis with secondary erosion of cartilage, etc., are apt to follow, and thus permanent interference with movement may result. Spontaneous hæmorrhages occur also from mucous membranes, such as those of the nose, alimentary and urinary tracts, etc., but the skin petechiæ met with in purpura do not occur. The tendency to bleeding often diminishes in the later years of life. Hæmophilia, which represents a congenital defect, is, in its typical form, practically restricted to the male sex and has a clearly hereditary character, striking examples of families of bleeders being known. Another important fact is that the disease is transmitted ordinarily through a female carrying the defect. It is regarded as a Mendelian recessive factor. These facts will be understood from the following account.

Hæmophilia is regarded as the result of the absence of a gene controlling blood coagulation. This gene is carried by the X sex chromosome; and in a small proportion of individuals it is absent as a mutation. In the female the abnormality (X′) is represented by XX′, and the normal X is sufficient to prevent the bleeding tendency; such a heterozygous female is not hæmophilic. The male sex chromosome Y does not carry the gene and accordingly an X′Y male is a hæmophilic. The union of a hæmophilic male with a normal female never results in hæmophilia—there is always one X to prevent it. The only possibility of a hæmophilic female arises from the union of a hæmophilic male with a female carrying the gene abnormality, i.e. XX′. In such a case X′X′ or X′Y′ (hæmophilics) might then occur in the offspring. Such a union must be very rare, though it might occur from intermarriage in a hæmophilic stock.

In hæmophilia there is comparatively little change in the corpuscular elements of the blood; the number of leucocytes is usually somewhat diminished, the fall being on the part of the polymorphonuclears. The blood platelets show no diminution in number such as is common in purpura. The *coagulation time* of the blood, when estimated between the bleedings, is greatly lengthened—according to Almroth Wright's results, up to an hour by the capillary tube method. After a bleeding, however, the coagulation time becomes shortened and may approach the normal; this is in accordance with the more rapid coagulation which occurs as a physiological response after hæmorrhage. The bleeding time is usually normal. This is usually explained as being due to the fact that in a wound such as a prick, the bleeding from the capillaries is stopped by platelet accumulation, for which the supply in hæmophilia is sufficient.

An abnormality in the platelets was first described by Minot and Lee. In hæmophilia the platelets in shed blood become altered in appearance and fuse together much more slowly than those of normal blood. The addition of normal platelets to hæmophilic plasma causes it to coagulate in normal time, whereas the platelets from a hæmophilic case have much less effect even when added in larger amount. There accordingly seems to be an abnormal stability of the platelets, as a result of which they undergo change and liberate thrombokinase unduly slowly. This is in accordance with the results of Sahli and others that the delayed coagulation is due to a deficiency of thrombokinase, and it is possible that this may apply to that supplied by the vessel wall as well as that by the platelets. The tendency to the occurrence of serous effusion and hæmorrhages in hæmophilia certainly points to the existence of a vascular abnormality. The view that platelet abnormality is the essential factor in hæmophilia has, however, not yet carried general acceptance.

Purpura. This term is applied in a general way to conditions where there are multiple small hæmorrhages into the skin, mucous membranes and internal parts of the body ; there may be also hæmorrhages from mucous surfaces. We have mentioned above (p. 23) a number of the pathological states in which such extravasations are met with, and we may recall that they are chiefly toxic or infective conditions, on the one hand, or diseases of the blood on the other. Accordingly this secondary purpura may be produced in various ways ; it is a symptom rather than a special disease. But whilst this is so, purpura occurs without evidence of its being secondary to the conditions mentioned ; it may be of a comparatively mild form—*purpura simplex,* or it may be a severe disease attended by extensive bleedings and fever, and often leading to a fatal result—*purpura hæmorrhagica*. It is now recognised that cases of purpura fall into two main classes, namely (*a*) those with little or no fall in the platelet count, and (*b*) those in which there is a distinct fall—essential thrombocytopenia or thrombocytopenic purpura. To the former group belong most cases of simple purpura, e.g. Henoch's purpura, rheumatic purpura, and Schönlein's purpura, and many of these are believed to be of allergic nature (p. 194), often called anaphylactoid. The following are the essential features of the thrombocytopenic type.

Thrombocytopenic purpura, which is known also as Werlhof's disease, occurs in acute and chronic forms, the latter being the commoner. The number of the platelets may fall to 10,000 per c.mm., or even less, and they often show abnormalities in size and in shape. There is usually little or no increase in the coagulation time of the blood outside the body, but the *bleeding-time*, that is, the time during which bleeding occurs from a prick or small wound, is much prolonged. The coagulum formed in extra-vascular clotting has the peculiarity that it does not retract from the wall of the container. Apparently this depends on the paucity of platelets, though they can cause the formation of clot in the usual time. In a considerable proportion of cases splenectomy is followed by a remarkable improvement.

This has been specially so in chronic purpura with exacerbations, but even in acute cases with marked anæmia the result may be very striking. In the latter, excision of the organ should be preceded by transfusion. The operation may be followed not only by disappearance of the purpuric state but by a rapid increase in number of platelets, in some cases up to normal. At the same time, the bleeding time becomes shortened and the blood coagulum shows the feature of ordinary retraction. There is often also a remarkable reticulocyte response with rise in the number of erythrocytes. In some cases relapse has been recorded, but undoubtedly in many instances the favourable effect has lasted for some time and probably is permanent. Recently it has been found by Troland and Lee that from the spleen of a thrombocytopenic there can be obtained an extract which has a remarkable effect in lowering the platelet count. Similar extracts from spleens in other conditions had no such effect. These results along with the effects of splenectomy in the disease indicate that the essential abnormality is in the spleen rather than in the bone-marrow. A definite statement, however, cannot yet be given.

Some abnormality of the capillary endothelium is apparently present in this type of purpura, as is sometimes shown by a tendency to hæmatoma on slight bruising, and it seems that in some unknown manner this is related to the deficiency in platelets. An abnormal state of the vascular endothelium in purpura is also indicated by the fact that if the venous return be obstructed by applying a tourniquet or tight bandage to the arm, small petechiæ tend to form in the congested area below. It may be mentioned that in primary aplastic anæmia (p. 468) we have another disease in which marked thrombocytopenia is associated with purpuric eruption.

We may refer to the important work of Ledingham, who showed that the injection of an anti-platelet serum produces a markedly purpuric condition in guinea-pigs, as well as a rapid fall in the number of platelets. Bedson, in investigating this phenomenon, found no evidence that the hæmorrhages are due to platelet thrombosis, and he came to the conclusion that the serum produces some slight lesion of the vascular endothelium. There is clearly an intimate relationship between paucity of platelets and an abnormal condition of the walls of the capillaries, as shown by the tendency to petechial hæmorrhages.

Scurvy. This disease, in which the hæmorrhagic tendency is a well-marked feature, has for long been recognised as due to deficiencies in diet, especially fresh vegetables and fruit. It used to be common during long sea voyages, and it has occurred in severe form during war amongst the inhabitants of beleaguered towns. Cases of mild scurvy are occasionally met with in civil life amongst the poorer classes, while infantile scurvy is by no means a rare affection. The changes in the bones and the other features of the latter condition are described later (p. 830). The anti-scorbutic property in vegetables, etc., depends upon the presence of a comparatively unstable accessory food principle, 'vitamin C'; organic acids in themselves have no protective properties. Scurvy is characterised by the occurrence of petechiæ in the skin, hæmorrhages or sanguineous effusions under the skin, in the muscles, under the periosteum, and into the joints, the lower limbs being most frequently affected. Another characteristic feature is swelling and sponginess of the gums, especially around carious teeth, and later there may be extensive ulceration with fungous granulations. Hæmorrhages from the mucous membranes are met with in severe cases. There is lowering of the resisting power of the tissues, and the subcutaneous swellings may be the seat of ulceration which may be both multiple and extensive; inflammations of serous membranes attended by blood-stained effusion are not infrequent. In scurvy there is no abnormality in the coagulation of the blood or in the number of the platelets. Anæmia of microcytic type is often present and this is as a rule readily amenable to treatment by vitamin C.

A condition of scurvy, with all the essential features, can be readily produced in animals, notably guinea-pigs, by feeding them with a scorbutic diet, e.g. one composed of cereals and water, to which autoclaved milk may be added; and by this method the distribution and properties of the anti-scorbutic factor have been further defined. The following are some of the results obtained by workers at the Lister Institute. The anti-scorbutic principle is most abundant by far in green vegetables and in citrous fruits, notably in lemons and oranges; in limes, on the other hand, it is much less abundant. The juices of vegetable roots vary considerably, but the juice of the swede turnip is very effective. The principle is relatively unstable and is readily destroyed by drying; green vegetables when dried have been found to have practically no preventive action. It is destroyed also by heat, and vegetables heated in water over an hour even at 70° C. lose much of the preventive property. In these respects there is a contrast to the anti-neuritic factor (p. 799). A noteworthy feature is that fresh meat and milk have only a very slight anti-scorbutic value. Another point of interest is that whilst cereals and pulses have no protective action in the dried condition, they acquire this property when they are placed in water and allowed to germinate for a few days. The presence of the anti-scorbutic factor accordingly appears to be associated with the metabolic processes of active vegetable growth.

Paroxysmal Hæmoglobinuria. The passage of hæmoglobin in the urine is seen in certain poisonings, e.g. poisoning with chlorate of potash, and is the characteristic feature of blackwater fever (p. 474). A paroxysmal form is met with, however, and in the commonest type its occurrence is definitely related to the direct action of cold. Ehrlich showed that if the finger of a person suffering from this affection is compressed at the base so as to obstruct the circulation, and then placed in cold water for a time, the serum of the blood afterwards withdrawn from the part shows distinct staining with hæmoglobin.

The essential feature of the disease is thus a lysis of the corpuscles in the circulation, the hæmoglobinuria being, of course, secondary. Further, it has now been established that this lysis is due to the action of a hæmolysin, involving the action of an immune-body and complement, such as has been described above. The interesting fact is that this immune-body, though present in the blood of the patient, does not unite with the red corpuscles at the temperature of the body, but does so when the temperature is lowered. After the combination has taken place, the corpuscles undergo lysis by the action of complement normally present. This is known as the Donath-Landsteiner reaction. The action of cold in bringing about attacks of hæmoglobinuria has thus received an explanation, and it may be added that another favouring circumstance is the occurrence of local vascular disturbances leading to venous congestion and cyanosis, such as are met with in Raynaud's disease. The application of the Wassermann reaction has shown that syphilis is present in the vast majority of cases ; in fact, it is probable that this form of paroxysmal hæmoglobinuria is always the result of syphilitic infection. In cases where the affection has lasted for some time siderosis may be present in internal organs ; we have found this to be specially marked in the kidneys.

Nothing definite is known as to the origin of the substance like an immune-body, which brings about lysis ; there is no evidence that it is produced by a previous abnormal destruction of red corpuscles. It has been shown in recent times that a hæmolytic immune-body may be developed by the injection of substances other than the corresponding red corpuscles. For instance, such a hæmolysin, known as *heterologous*, may be produced for sheep's corpuscles by injecting the rabbit with an emulsion of the adrenals or other organs of the guinea-pig. The antigens which stimulate the formation of heterologous immune-bodies are related to lipoidal substances, and it is possible that lipoids or other products of tissue disintegration in syphilis, may be active agents in leading to the formation of the lysin.

Another form of paroxysmal hæmoglobinuria has no relation to cold, but occurs after muscular exertion. No hæmolysin has been detected in the blood in this type, and no relationship to syphilis has been established. It has sometimes been attended by stiffness and even by induration of the muscles, and is probably allied to the paroxysmal hæmoglobinuria which is not uncommon in horses when exercised after a long period of rest. In the latter condition the hæmoglobin is generally believed to be derived from the muscles, but the exact nature of the condition is unknown.

CHAPTER XII

HÆMOPOIETIC SYSTEM (*continued*)

SPLEEN, LYMPHATIC GLANDS, BONE-MARROW

THE SPLEEN[1]

No organ in the body undergoes in disease so great variations in size as the spleen. An atrophied spleen may weigh only two or three ounces, whereas the weight of the organ in leukæmia and other conditions may reach five pounds or more. And as enlargement can be readily detected during life, an intelligent knowledge of the causes producing it is of great clinical importance. We shall use the term 'enlargement,' as, although increase in size may represent a functional hypertrophy, this is not always so, and in some conditions the cause is unknown.

Atrophy of the spleen occurs in old age, and is aided by conditions of inanition and by arterial disease. When an atrophied spleen is examined *post mortem*, its capsule is found to be thicker and more opaque than normally and sometimes wrinkled, and on section the trabecular tissue is seen to be increased and to stand out distinctly against the pulp ; the artery walls are often somewhat prominent and sclerosed. There is atrophy of the pulp and of the Malpighian bodies, the latter sometimes being scarcely distinguishable.

Splenic enlargement may be regarded in great part as an expression of increased functional activity of the spleen as a large reticulo-endothelial organ and blood reservoir. Apart from the formation of lymphocytes and probably also monocytes, its function is of the nature of phagocytosis, destruction and storage. Thus the main enlargements are seen in infections, in certain blood diseases and in certain conditions of abnormal metabolism. There are also causes such as amyloid disease, chronic congestion, etc., to which reference will be made. We shall first consider in a general way the main causes of enlargement met with and the resulting changes.

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[1] For a detailed account with bibliography, see *The Spleen and Anæmia,* by Pearce, Krumbhaar and Frazier, Philadelphia and London, 1917 ; *Die Erkrankungen, der Milz,* by H. Hirschfeld, Berlin, 1920 ; *Die Hepatolienalen Erkrankungen,* by H. Eppinger, Berlin, 1920 ; *La rate, organe réservoir,* by Leon Binet, Paris, 1930 ; and *Die normale und pathologische Physiologie der Milz,* by E. Lauda, Berlin, 1933.

Splenic Enlargement in General

The vascular arrangements of the spleen are of great importance in connection with its functions both in health and disease. Histological investigation has shown that the arteries break up into delicate vessels which terminate in two chief ways. The blood from some passes into the venous sinuses, while that from others passes through the reticulum of the pulp before doing so. A third may be added, namely that through the capillaries of the Malpighian bodies, the blood thereafter passing into the venous sinuses. The important point is that there are two main circuits of blood flow, a short and a long. This vascular arrangement has been demonstrated in a striking way from the physiological side by Barcroft and his co-workers. Their general result is that the pulp of the spleen forms a sort of backwater or reservoir in which the blood is relatively at rest in normal conditions. When, for example, carbon monoxide is administered to a resting animal there is a lag in the combination of the gas with hæmoglobin in the spleen, an interval of about thirty minutes elapsing before the amount of CO-hæmoglobin in the spleen corresponds with that in the blood. The splenic pulp thus contains an amount of relatively stagnant blood, and this may be added to the circulating blood by contraction of the organ. Such contraction occurs after hæmorrhage and in conditions of anoxæmia when there is a demand for additional hæmoglobin in the circulation. This backwater in the spleen is of great importance in pathological conditions, and its action as a reservoir for meeting abnormal requirements is the basis of many cases of enlargement.

In connection with the vascular arrangements, important structures are the ellipsoids connected with the fine penicillar arterioles near their terminations. These are spindle-shaped bodies in the course of the vessels, formed by replacement of the muscular tissue of their walls by cells of endothelial type, between which blood can pass into the surrounding pulp. The blood in the arterioles has thus two possible courses, one a short route directly onwards, and another longer route through the ellipsoids. The latter apparently are contractile and have a valve-like action. In acute enlargements, the blood passes through them and leads to a general distension of the pulp. The ellipsoids are sometimes the seat of pathological changes, e.g. hæmorrhage with subsequent fibrosis in splenic anæmia, as has been described by McNee and others. Details of structure vary in different animals and there is still controversy on certain points. Robinson, for instance, considers that there are no communicating channels between the arteries and the veins except through the pulp spaces. The main facts with regard to the double circulation have, however, been established.

(*a*) Enlargement occurs in a variety of *infections*, and these may be of bacterial or protozoal nature, and of acute or chronic character. Organisms of these two different kinds accumulate in the splenic pulp, and the enlargement is in great part due to reactive changes concerned in their destruction. In this respect a close parallel can be drawn between the spleen and the lymphatic glands ; the former has pretty much the same relation to the blood stream as the latter have to the lymph stream. In each case the structure is so arranged that the stream is slowed and is exposed to the phagocytic action of endothelial and other cells; opportunity is thus given for the separating out of abnormal elements and their subsequent destruction or storage.

In acute infections, the earliest change in the spleen is probably an acute congestion or engorgement brought about through the vasomotor mechanism by the action of toxins on the tissue of the organ. In this way an increased amount of blood is brought under the influence of the phagocytes of the organ, which soon show proliferative and increased functional activity; polymorpho-nuclear leucocytes also may be attracted to the organisms which accumulate in the splenic pulp. By such a mechanism not only bacteria and other parasites are removed and accumulate in the splenic pulp, but also damaged red cells and leucocytes. Red corpuscles are often taken up by macrophages, within which they are disintegrated, with the formation of hæmosiderin as the ultimate result. Phagocytosis of injured polymorpho-nuclears also may occur, though it is not so common as in the sinuses of lymphatic glands; it is found more frequently in the lower animals than in the human subject. These leucocytes are not numerous in the pulp in the normal state, but in septicæmic conditions, for example, they gather in large numbers and many undergo extracellular degeneration; and the proteolytic enzymes which they contain cause the post-mortem autolysis and softening which are often marked in such conditions. The macrophages are chiefly derived *in situ* from the endothelial cells of the venous channels and the reticulum, these becoming separated and undergoing proliferation. They are added to by the monocytes of the blood.

When the processes described have lasted for some time, as in chronic infections, there occurs reaction on the part of the stroma of the organ as the result of toxic action, and possibly also of abnormal products of metabolism. The organ then becomes increased in consistence and even indurated, as is well seen in cases of chronic malaria and kala-azar.

(*b*) The part played by the spleen in *blood destruction* is recognised to be of great importance. The cells of the reticulo-endothelial system have the power of forming from hæmoglobin both iron-containing pigment and also bilirubin. Little is known with regard to the normal metabolism of the iron compounds, except that the iron is used again in blood formation. In conditions of disease, however, blood destruction within the spleen is often a prominent feature and deposits of hæmosiderin result. The pigment is found both in free macrophages and within endothelial and reticular cells still in position. The function of the spleen in blood destruction is found to occur sometimes in exaggerated form, so that benefit is obtained by the removal of the organ. This has been found to be the case especially in acholuric jaundice and in some cases of splenic anæmia (p. 498). Further, when there is a great excess of leucocytes or of red corpuscles in the general circulation there is an attempt to deal with the excess in a similar way, a certain proportion of the cells being retained in the spleen; hence the great splenic enlargement met with in leukæmia and polycythæmia.

The spleen has also an important relationship to *blood platelets*, but this subject also is still very obscure. It has been established, however, that in purpura with deficiency of platelets in the blood, the removal of the spleen is often followed by disappearance of the purpura and a great increase of the platelets (p. 486).

(*c*) The spleen acts as a storehouse of fats and lipoids when they are present in excess, these substances being taken up by the cells of the reticulo-endothelial system. Such a storage occurs in cases of diabetes with lipæmia and in some cases of jaundice. The outstanding example, however, is the storage of lipoids which occurs in Gaucher's and in Niemann's disease, the lipoidal accumulation in these conditions leading to enormous enlargement of the organ (p. 499).

Whilst the splenic pulp has primarily destructive or storage function in certain conditions, myeloid tissue may be formed in it from the reticulo-endothelial cells and will thus be the source of both erythrocytes and granular leucocytes. This 'myeloid transformation' as it is called is met with in various anæmic conditions referred to above.

Splenic Enlargement in Infections

The infections leading to splenic enlargement may be classified as follows; I. Bacterial infections, (*a*) acute, (*b*) chronic, and II. Protozoal infections. These will now be considered in this order.

I. BACTERIAL INFECTIONS, (*a*) *Acute*

Acute Splenic Enlargement or Swelling. This appears the most convenient designation of the condition produced. It is often called acute congestion, but the organ may contain a smaller proportion of red corpuscles than normally. The enlargement, of course, varies much in degree; the colour of the organ may be pale or dark red, the consistence soft or practically normal. A striking type is what is often called 'septic spleen.' It occurs in *septicæmic conditions*, especially those due to streptococci. The organ is swollen and soft, and on section it has a pinkish creamy appearance, while its substance may be almost diffluent and the structural outlines may be quite gone. Such a condition, though initiated during life, is greatly increased *post mortem* by autolytic changes. Organisms can usually be found on microscopic examination, and in streptococcic cases may be very numerous. We have always found polymorpho-nuclear leucocytes in considerable numbers, and, as has been said, the softening is probably due to enzymes formed by them, which act on the splenic tissue damaged by bacterial toxins. When a case of septicæmia is of subacute character, the splenic enlargement becomes more marked, though the tissue is not so pale and soft. A striking example is seen in *subacute bacterial endocarditis* due to non-hæmolytic streptococci, where the organ may weigh as much as two pounds. On section, the splenic tissue has usually a dull pinkish colour, with indistinct Malpighian bodies, and the substance is a little softer than the normal ; the condition may, of course, be associated with infarctions. We mention specially the enlargement of the spleen in bacterial endocarditis, as it is not generally realised how great a degree this may reach.

In *typhus fever* the spleen is usually enlarged, pale and soft, as it is also in severe suppurative or confluent *smallpox*, though in the latter disease the change is possibly due to streptococcic infection which is of common occurrence. In rapidly fatal cases of hæmorrhagic smallpox, in which there is often leucopenia with marrow elements in the blood, the spleen is usually of dark red colour and contains many of the elements of the marrow which have been swept into the circulation. In *typhoid* fever splenic enlargement is an important feature, the weight sometimes reaching a pound or over, but the organ is not pale or much softened. In our experience it is usually of a fairly uniform reddish colour and of moderate consistence, or it may be deep red owing to congestion. The colour depends, of course, on the proportion of leucocytes and red corpuscles, the former, as in other typhoid lesions, being chiefly mononuclear cells and lymphocytes. Typhoid bacilli usually occur in clumps in the pulp, and though there is sometimes necrotic change around them, they may be unattended by any sign of damage in their neighbourhood.

Undulant fever and *relapsing fever* are diseases in which there occurs considerable splenic enlargement without much softening of the septic type, and in both of them the causal organisms abound in the splenic pulp. In the former, the enlargement becomes more marked as the disease goes on ; the average weight has been found to be a little over a pound, but much greater degrees of enlargement are met with. Metchnikoff showed that in relapsing fever at the time of crisis when the spirochætes disappear from the blood, they accumulate in the pulp and become the prey of phagocytes. Whilst this is the mode of destruction of the spirochætes, the essential factor in the production of the crisis is the development of antibodies in the blood, which have an antagonistic action on the organisms and lead to the occurrence of phagocytosis. The importance of the spleen is exemplified by the fact that animals which merely suffer from a single attack on inoculation, may have relapses when the organ has been removed.

The condition of the *Malpighian bodies* varies in the several infections referred to. In some they are enlarged and distinct, while in others they are little changed (in the pale soft spleens they are often indistinguishable by the naked eye). A not uncommon change is an increased prominence of the germ centres with fragmentation of the nuclear chromatin, some being distinctly necrotic. It would appear as if the toxin present acted first as a mild irritant with resulting proliferation and later killed the cells. Such changes are common in scarlet fever and diphtheria, especially in children ; and they are occasionally met with in other infections.

Suppuration. Abscesses in the spleen are not very common ; they are usually of fairly large size, and of the type of septic infarcts. They occur in such conditions as acute bacterial endocarditis, pyæmia, etc., and are sometimes secondary to abscesses in the lungs ; they are usually accompanied by considerable enlargement of the organ. The suppurative process starts at the margin of the infarcted areas and extends through their substance ; occasionally they have a gangrenous character, the pus being foul-smelling. An abscess involving the capsule, as it usually does, is associated with perisplenitis, and this may give rise to perisplenic abscess. Minute abscesses, such as are common in the kidneys, are very rare in the spleen. In general infections due to staphylococci and streptococci the organisms accumulate in the pulp of the spleen, and many are destroyed. They seem to have little power of producing actual suppuration, unless they are contained in emboli which give them a foothold. By the action of their toxins on the splenic reticulum a certain amount of softening may be produced, as described above.

I. Bacterial Infections, (*b*) *Chronic*

Tuberculosis. In tuberculous affections bacilli are often carried by the blood to the spleen, and its tissue seems relatively susceptible to their action ; accordingly, tubercles in this organ are of comparatively common occurrence. In acute miliary tuberculosis the tubercles are specially numerous in the spleen. They generally appear as minute grey points of about the size of Malpighian bodies, though sometimes they are larger and of yellowish tint. When they are minute it is sometimes difficult to distinguish them from Malpighian bodies, but if the light is allowed to fall obliquely on the cut surface the tubercles can usually be seen to project somewhat from it. In children the spleen is occasionally studded with yellowish tubercles of about the size of small peas—a condition of subacute tuberculosis (Fig. 311). But apart from general infection it is not uncommon to find in cases of phthisis, tuberculosis of bone, etc., a few tubercles in the spleen. These are of varying size, and occasionally larger nodules or collections of nodules may be present—conglomerate tubercle. Further, there occur cases where the spleen is greatly enlarged and contains collections of tubercles and caseous masses which are sometimes associated with pale infarctions, apparently the result of obliteration of arterial branches ; in such conditions the cut surface presents a very variegated appearance. A rare type of tuberculous (?) lesion is described in connection with splenic anæmia (p. 499).

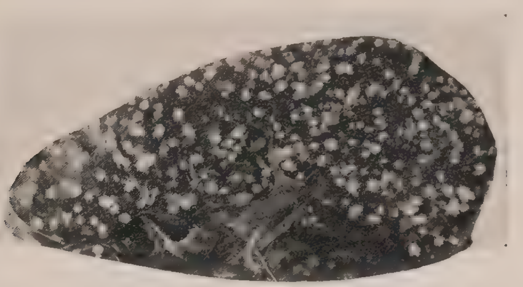

Fig. 311.—Subacute Tuberculosis of Spleen of Child, showing numerous and fairly large caseous nodules. × $\frac{3}{4}$.

Syphilis. Syphilitic lesions in the spleen are somewhat uncommon and difficult to distinguish. In congenital syphilis the spleen is often swollen and contains numerous spirochætes, and thickening of the stroma or diffuse fibrosis may result ; miliary gummata have been described, but they are very rare. In tertiary syphilis in the adult, gummata may occur, but are distinctly rare. They are sometimes wedge-shaped and may be like pale infarcts in appearance. Amyloid disease of the spleen is not infrequently produced by syphilis.

II. Protozoal Infections

The outstanding examples of splenic enlargement due to these infections are seen in malarial fever and in kala-azar. In *malarial fever* swelling of the spleen occurs with each attack of pyrexia, and is to be regarded, as in the case of bacterial infections, as an acute congestion due to the accumulation of parasites in the organ ; in chronic cases considerable enlargement may result. For a long time the spleen is little altered in appearance, but thickening of the stroma with induration may ultimately occur and the organ may reach a large size. It becomes firm in consistence and may have a brownish-grey colour owing to accumulation of malarial pigment—the term ‘ ague-cake ’ is applied to such a large indurated spleen. The weight of the organ may reach two or three pounds, but such large spleens met with in the tropics are not so often due to malaria as was formerly supposed, since many are the result of the more recently recognised disease, kala-azar.

In *kala-azar* great enlargement of the spleen is common, the organ not infrequently being several pounds in weight, and its stroma tends to become much indurated. There is great increase of the stroma, and the meshwork of the pulp is largely occupied by collections of macrophages which contain the parasites known as 'Leishman-Donovan' bodies. These can be readily found, as a rule, by means of splenic puncture, and a diagnosis can thus be made. The parasites occur in the form of rounded or oval bodies, sometimes of cockle-shell shape, which measure up to 3·5 μ in diameter, though most of them are smaller. Each contains two structures composed of chromatin, the one being larger and somewhat rounded in form, the other more rod-shaped. These two structures represent the macronucleus and the micronucleus of the parasite respectively, as is shown in the further development of the parasite which can be followed in culture media outside the body.

Splenic Enlargement in Blood Diseases, etc.

Several of these have already been described, but we may recapitulate some of the chief points, especially in relation to diagnosis. Great enlargement is met with in the following conditions, viz. : (*a*) in leukæmia and pseudo-leukæmia ; (*b*) in lymphadenoma ; (*c*) in polycythæmia ; (*d*) in splenic anæmia ; acholuric jaundice.

In **leukæmia** the most marked enlargement occurs in chronic cases, especially in the myeloid though also in the lymphatic type, and the spleen may form a huge palpable mass. The condition of the blood will establish the diagnosis if leukæmia is present (p. 475). In *pseudo-leukæmia* the splenic enlargement is associated with enlargement of the lymphatic glands, while the leucocyte count may be normal or there may be a relative lymphocytosis. At a later period, however, the blood changes of lymphatic leukæmia may develop. The condition of the spleen is usually the same as in lymphatic leukæmia, though the enlargement is rarely very great. In some cases, however, the enlargement is due to a great hyperplasia of the Malpighian bodies, which form small rounded nodules. It is not possible, however, to explain the occurrence of this somewhat exceptional condition.

In **lymphadenoma** the size of the spleen varies greatly. In some cases it is hardly enlarged, in the majority it is moderately so ; whilst, again, in a few the enlargement may be considerable (p. 509). It is associated with enlargement of lymphatic glands, and the condition of the leucocytes may be practically normal, or some leucocytosis may be present. In early cases only microscopic examination of lymphatic glands can supply a diagnosis.

In **splenomegalic polycythæmia** the degree of enlargement varies considerably ; it may be comparatively slight, but, on the other hand, it may be very marked and the organ may form a large firm mass easily palpable during life. The change consists in a packing of the pulp with red corpuscles and appears to represent an attempt to deal with the excess of corpuscles in the circulation, the spleen acting as a sort of reservoir. There appears to be little evidence of blood formation in the organ. Examination of the blood will, of course, reveal the nature of the condition (p. 483).

The Spleen in Splenic Anæmia. The group of anæmic conditions associated with splenic enlargements, is badly defined and imperfectly understood; and the etiology (apart from malarial and kala-azar cases) is unknown. The term 'Banti's disease' is sometimes used as synonymous with splenic anæmia, but in the condition described by him the anæmia and splenomegaly are associated with cirrhosis of the liver of the atrophic type. According to Banti's description the cirrhosis is the last phenomenon to appear, and leads to symptoms of portal obstruction. It is generally agreed now that splenic anæmia is an anæmia associated with hepatolienal fibrosis, the spleen and liver being affected in varying degree. Banti's disease is merely a syndrome of the condition. The anæmia is of the hypochromic type, usually attended by leucopenia (p. 464).

In *splenic anæmia* the spleen may reach a great size, though its weight is not often over three pounds. The capsule is often thickened and adhesions are not uncommon. In some cases the organ contains a relatively large amount of blood, which, from a spleen excised during life, readily flows out, leaving the organ somewhat collapsed. In most instances, however, especially those of longer standing, the consistence is firm and may even be tough, the colour is a moderately dark red, and there is apparently hyperplasia of the pulp. The Malpighian bodies are as a rule fibrotic and ill-defined, but may be quite distinct. In a considerable proportion of cases in children as well as in adults, the so-called 'siderotic nodules' are present. These are of the size of pin-heads or much larger, and somewhat irregular in form; they often show a yellowish centre surrounded by a brown zone. *Microscopic examination* shows usually a considerable amount of fibrosis of the spleen. This is specially related to the small arteries, extending from them into the surrounding pulp; it is often marked around the Malpighian bodies which may be largely fibrotic. There is also sclerotic thickening of the walls of arteries. The sinuses are usually dilated and there is often a general thickening of the reticulum of their walls or even fibrosis (Fig. 312). Sometimes these changes are little in evidence and there is merely a general hyperplasia of the splenic pulp. Hæmorrhages around the small arteries are common and all transitions between these and the siderotic nodules may be present. The latter contain much granular hæmosiderin and also jointed yellowish filaments which give an iron reaction—apparently deposits of iron-containing material around fibres. The dense connective tissue around may give a diffuse iron reaction. These fibrotic nodules are the result of hæmorrhage around penicillar arteries, the blood afterwards undergoing the usual changes with accompanying fibrosis. McNee regards them as hæmorrhages into ellipsoids as a result of backward pressure, these structures having a valve-like action and thus being specially exposed to the pressure. They are not peculiar to splenic anæmia, being also met with, for example, in acholuric jaundice.

The walls of the dilated splenic and portal veins are often thickened and may be the seat of atheroma-like plaques; in a considerable number of cases thrombosis has been present. This may actually be the cause of enlargement of the spleen in some cases considered to be splenic anæmia, but often there is no thrombosis, and this explanation cannot be generally applied. The bone-marrow in splenic anæmia is often markedly hyperplastic, but without any special feature. Hæmorrhage from the stomach is a common feature, and results from portal congestion, often clearly indicated by varices at the lower end of the œsophagus.

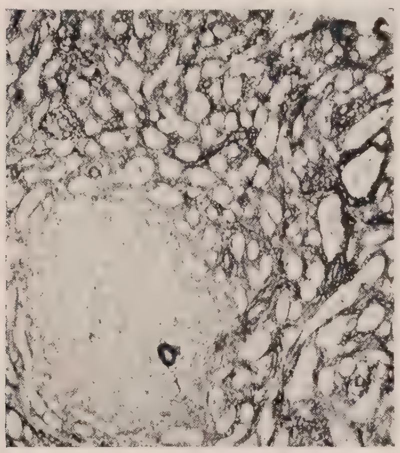
Fig. 312.—Spleen in splenic anæmia showing general increase of reticulum in pulp. A Malpighian body in field is unaffected. (A. C. L.) ×80.

The various changes in the spleen, hæmorrhages, etc., and the frequent bleeding from the stomach indicate there is increased pressure in the portal circulation. This might result from cirrhosis or hepatitis when present, and in cases where they are absent it has been ascribed to narrowing of the branches of the portal vein or even to a supposed contraction of the branches. It seems very doubtful, however, whether the splenic enlargement can always be due to such causes and the appearances rather point to some irritant which acts on the tissues of both spleen and liver. The fact, too, that removal of the spleen by operation is often followed by improvement, if not cure, indicates that there may be some agency in the spleen which produces an injurious effect on blood formation. The real cause of the anæmia, however, is not understood. The condition of the platelets in relation to splenectomy has been referred to on p. 464.

The Spleen in Acholuric Jaundice. Splenic enlargement in this disease is usually marked but not excessive, the weight rarely exceeding 3 lbs. It is associated with increased fragility of the erythrocytes and excessive hæmolysis. The changes in the spleen and the other features of the disease have already been described in connection with diseases of the blood (p. 466).

Still another type of lesion is sometimes found in cases diagnosed as splenic anæmia, and this may be provisionally called the 'tuberculous type.' The greatly enlarged spleen may be studded with nodules and masses of yellowish tissue, or, as in a spleen recently excised which I examined, with groups of grey tubercle-like nodules not larger than millet seeds, uniformly disposed throughout the organ. In such cases the histological picture is like that of tuberculosis with well-formed giant-cell systems, endothelioid cells, etc.; usually there is little or no caseation. I was unable to find any tubercle bacilli in the tissue and this has been the result obtained by others. It is accordingly not possible to state definitely that the condition is really tuberculous.

Splenic Enlargement due to Lipoid Storage

It has already been mentioned (p. 149) that feeding animals with cholesterol in oil results in the deposition of cholesterol fat in the intima of arteries and storage in the reticulo-endothelial system. A similar storage of lipoids occurs in disease in two groups of conditions.

(*a*) One group includes definite diseases not infrequently associated with hypercholesterolæmia, viz. diabetes and obstructive jaundice. Marked deposit of lipoids of sufficient degree to cause enlargement of the spleen occurs only occasionally, but quite a considerable number of cases have been recorded. The cells of the pulp become enlarged owing to the lipoid accumulation, and the lipoids may be in globules which react variously with fat stains, or in a masked state apparently combined with protein. For example, cholesterol may be present in the spleen in increased amount without doubly refracting esters being detectable in the cells. Although the deposit occurs secondarily to hypercholesterolæmia it is not possible to state definitely what actually determines the large amount in certain cases.

(*b*) In the second group we have rare diseases often of familial and hereditary nature, such as those of the Gaucher and Niemann type, in which the lipoid storage becomes excessive in various tissues and the enlargement of the spleen is very great. It is usual to regard these conditions as the result of abnormal lipoid metabolism, but we know nothing of the essential defect. Moreover, the characters of the lipoids vary in different types.

Gaucher's Disease. This disease was described first by Gaucher in 1882, who regarded it as a type of new growth in the spleen, a view which has since been discarded. The number of recorded cases is still not large, but the disease is not of the rarity it was supposed to be. In a fairly large proportion of cases it has shown a familial character, two or more members of the family being affected. The disease is met with both in adults and in children, and as it is as a rule of very chronic character it is likely that it usually

Jm3.

starts in early life. The enlargement of the spleen may be extreme; in the adult the weight may reach ten pounds, while in a young child it may be a sixth of the body weight. The liver also often shows a varying degree of enlargement. The enlargement of these organs is due to collections of large cells of peculiar appearance. The cells have relatively small and sometimes eccentric nuclei which stain deeply; occasionally there are two or more nuclei in one cell. The protoplasm has a peculiar hyaline or reticulated appearance and sometimes contains small vacuoles (Fig. 313). In the spleen the cells occur especially throughout the pulp, though also within the Malpighian bodies, and they are apparently derived from the cells of the reticulum, the vascular endothelium being little changed (Fig. 314). In the liver they are derived from Kupffer cells and are most abundant in the centres of the lobules; replacement by connective tissue may occur and a certain amount of cirrhosis result. Similar collections of cells are often present in the lymphatic glands, especially those in the abdomen and thorax, and also in the bone-marrow. In the last-mentioned situation they may cause absorption of bone and spontaneous fracture, this sometimes being the first clinical sign. It may be added that the Gaucher cells may be sometimes found in the marrow on sternal puncture.

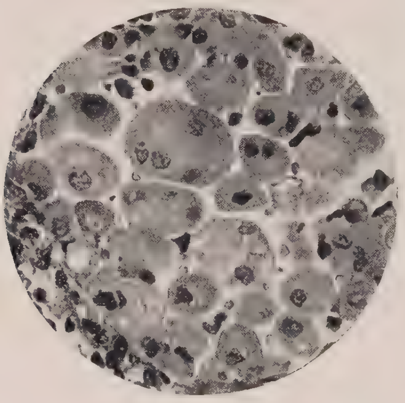

Fig. 313.—Section of Spleen in Splenic Anæmia of Gaucher type, showing the characteristic large Cells with granular Protoplasm. (Prof. E. H. Kettle.) × 300.

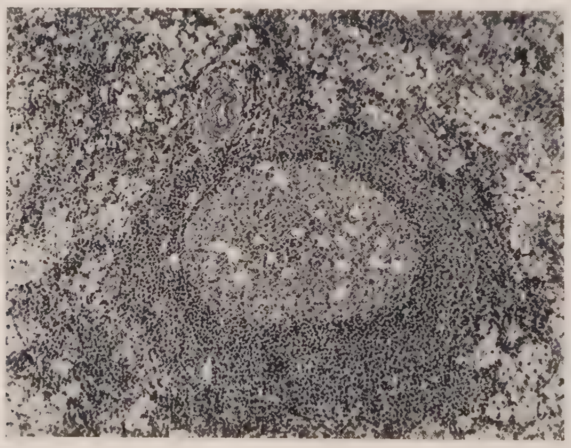

Fig. 314.—Section of Spleen of Child in Gaucher's Splenomegaly.

Collections of the large pale Gaucher cells are seen scattered in the pulp and a few are being formed in the germ centre of a Malpighian body. (J. W. S. B.) × 90.

The view now generally held, with which we agree, is that the essential feature of the disease is an infiltration of cells of the reticulo-endothelial system with lipoid material, with subsequent hyperplasia of these cells. The cells do not contain ordinary neutral fats; they give a varying and imperfect reaction with stains for lipoids. The affected tissues have been found on analysis to contain a considerable amount of cholesterol and lecithin, probably as part of some complex. Blacklock made the interesting observation that when sections of the spleen are heated in water at 100° C. the cell protoplasm comes to contain doubly-refracting globules like myelin. According to Lieb the substance stored in cells in Gaucher's disease is kerasin, a cerebroside.

Niemann's disease. This affection, also known as Niemann-Pick's disease, is another example of abnormal lipoid storage; though closely allied to Gaucher's disease it is regarded as distinct from it. It is a very rare condition met with in the first two years of life and is soon fatal as a rule. The storage of the lipoid is very extensive, occurring in the intestinal mucosa, adrenals, lungs, pancreas, etc., as well as in the liver and spleen, and there is also an accumulation in the histiocytes of the ordinary connective tissues. The lipoid stains more readily with fat stains than in Gaucher's disease and there is no doubt that it is of different nature; it is believed to be a phosphatide.

Schüller-Christian's disease is another example belonging to the same class; it also occurs in the early years of life and the lipoid concerned has been found to be mainly cholesterol ester. The affection is not infrequently accompanied by xanthomatosis of bones (p. 837).

Other Causes of Enlargement

Passive Hyperæmia. A distinction should be made between this condition as occurring in general venous congestion and that produced by portal obstruction, since the changes differ considerably in the two cases. In the former type, as met with in chronic heart or lung disease, the spleen becomes enlarged, but only to a moderate degree, its weight not often exceeding 8 oz., and it becomes markedly increased in consistence. On section, the cut surface is smooth and firm and the pulp is seen to be of dark purple colour, against which the Malpighian bodies and trabeculæ stand out prominently. Histologically, the chief change is due to the fact that the pulp has been opened out by the venous sinuses, which are more prominent and appear more numerous than normally. There is some thickening of the connective tissue of the trabeculæ and of the finer fibrils, and the elastic tissue also has been found to be increased. All these changes are to be regarded simply as the result of chronic overdistension of the organ. In cases of passive congestion affecting the *portal circulation*, as occurs in cirrhosis of the liver, the condition is somewhat different. The enlargement is much greater than in the previous form, the spleen being often considerably more than one pound in weight, whilst the consistence is often not increased. The organ on section has usually the ordinary colour or may be somewhat paler, and the pulp is in a condition of general hyperplasia with increase of cellular content, and may be even somewhat softened; the Malpighian bodies are usually indistinct. In fact, although chronic congestion is present, the appearance rather resembles that met with in chronic infective or toxic conditions, and it has been suggested by some that the spleen is acted on by the same poison as causes the cirrhosis of the liver. On this point it is not possible to speak definitely, and the whole question as to the relation of splenic enlargements with cirrhosis of the liver is very obscure. (See also *splenic anæmia*, p. 497.)

Chronic passive hyperæmia may be produced also by pressure of tumours on the splenic vein, and actual obstruction of the vein, as sometimes happens, leads to intense engorgement of the spleen. The organ then often becomes the seat of multiple infarction-like hæmorrhages, and its size may be greatly increased.

Amyloid Disease. As already stated, this degeneration occurs in two main types, the *sago* and the *diffuse* form, and is, of course, met with in the conditions which cause general amyloid disease (pp. 153, 154). In the former type the enlargement of the spleen is not great, and the chief change is that the Malpighian bodies are swollen and stand out against the pulp as round structures of homogeneous and somewhat translucent appearance and of reddish-brown colour. The amyloid change affects the capillaries and the delicate reticulum of the Malpighian bodies, the lymphoid cells being displaced by the material ; ultimately the Malpighian bodies may be changed into almost homogeneous masses. The small arteries also are affected, though sometimes the central artery of the Malpighian body and a small zone of lymphoid tissue around it escape.

In the diffuse form the enlargement is much greater and the weight of the organ may reach two pounds or even more. The increase is especially in thickness, and the organ becomes much firmer so that it can be readily palpated during life. The cut surface shows an almost uniform glancing appearance, which has been aptly compared to that of smoked bacon ; the trabeculæ are somewhat thickened and prominent, but the Malpighian bodies are often indistinguishable. In this type the amyloid change occurs throughout the pulp affecting the reticulum and the walls of the sinuses, which are often considerably widened ; the endothelial cells lining the sinuses can be clearly seen to be unaffected. The arteries are often extensively involved, and sometimes also the periphery of the Malpighian bodies. The two types of amyloid disease occur as fairly distinct affections, but it is not possible to say why this should be the case.

Tumours

Both primary and secondary growths in the spleen are very uncommon. Simple tumours such as fibroma, osteoma, myoma, hæmangioma, and lymphangioma have been described, but are all rarities. Cysts of the spleen are occasionally met with. They are usually small and multiple, though occasionally one may reach a large size and form a fluctuating swelling on the surface. The contents are a clear serous fluid, but there may be an admixture of altered blood. They are regarded to be usually of lymphangiomatous origin.

Primary sarcoma and lymphosarcoma have been met with. Occasionally the lymphoid tissue is the seat of growth and there may be general enlargement of the Malpighian bodies which form nodules to lead to great enlargement of the organ. The cells concerned may be of the lymphocyte class or of the reticulum type. The growths correspond with reticuloses or reticulo-sarcomata (p. 255).

Secondary growths occur more frequently in sarcoma than in cancer, but even in the former they are much rarer than one would expect. Secondary growths of cancer occasionally occur, but their rarity is a striking feature. This fact has already been considered (p. 238). Melanotic growths are occasionally met with. The contrast between the spleen and the bone-marrow as regards the occurrence of secondary growths is very noteworthy.

LYMPHATIC GLANDS

In relation to pathological processes, it is important to bear in mind that the lymphatic glands consist essentially of two parts, viz. the lymphoid tissue proper with its follicles, and the lymph sinuses and paths. The former has a formative function, being concerned in the production of lymphocytes; while the latter are specially concerned in the destruction of organisms or damaged cells carried from the tissues, as the relatively slow lymph flow gives favourable opportunity for phagocytic action. In fact, the sinus system has pretty much the same relation to the lymph stream as the splenic pulp has to the blood stream. The cells of the adenoid reticulum react in the same way as the endothelial cells of the lymph sinuses and paths; both belong to the reticulo-endothelial system and, in addition to being the source of active phagocytes, exhibit in high degree the storage capacity of that system towards various dyes and other substances present in solution. It is to be noted that the germ centres are largest and most active in the early years of life; later they are less in evidence, whilst in old age there is marked atrophy of the whole tissue of the glands.

Lymphadenitis. If a gland in relation to an inflamed area be examined, polymorpho-nuclear leucocytes may be found in the sinuses, these cells having reached the gland by the lymphatics, and often with them some of the invading organisms may be present. The latter may be destroyed *in situ* by the leucocytes, and these in their turn are then taken up and destroyed by endothelial cells, which have become free and spherical in form and act as macrophages. If the infection is rather more severe, then vascular reaction occurs. The vessels become congested and leucocytes emigrate from them, overrun the gland substance, and engage in the destruction of the organisms. Such is the condition when, for example, in relation to a poisoned wound of the hand, the axillary glands are swollen and somewhat painful. The inflammatory reaction corresponds with that seen in other tissues, and the lymphocytes appear to play essentially a passive part. The organisms are often destroyed by the leucocytes and the inflammation then resolves. On the other hand, they may get the mastery and continue to multiply; the leucocytic emigration continues, the tissue of the gland gradually softens, and suppuration results. This may be attended by inflammation of the surrounding tissue and in it also suppuration may follow. Such changes are met with in poisoned wounds of various kinds and are usually caused by streptococci, sometimes by staphylococci. In *plague* there is a severe inflammatory reaction with infiltration of polymorpho-nuclears, brought about by the bacilli which are present in enormous numbers; this is attended by much hæmorrhage and œdema in the glands and in the tissue between them, and there is often considerable necrosis of the substance of the glands. The so-called bubo is simply an inflammatory mass consisting both of glands and the tissue around them. In *anthrax* the lesion is mainly an inflammatory œdema with a varying amount of hæmorrhage.

In *typhoid fever* there occurs a remarkable proliferation of the endothelial cells along the lymph sinuses and paths, which become distended with such cells, many of which contain cellular remains (Fig. 315 and p. 558). The cells of the reticulum react in a similar way and there is also an emigration of monocytes from the blood. Necrosis and autolytic softening may follow, but there is practically no reaction on the part of the polymorpho-nuclear leucocytes. If the necrosis is extensive, the dead tissue becomes inspissated and encapsulated. In the course of the resolution of *lobar pneumonia*, the bronchial lymphatic glands are active in disposing of the cells and their derivatives carried from the lungs (p. 73).

When a mild irritant acts on a lymph gland for some time, endothelial proliferation is often markedly in evidence, constituting what may be called a *catarrh of the sinuses*. Such a condition is often seen in the axillary glands in chronic diseases of the breast, and must not be mistaken for secondary cancer. Chronic irritation in course of time leads to a thickening of the stroma; sinuses become obliterated, and ultimately there may be marked fibrosis with atrophy of the lymphoid tissue.

The phagocytic action of the cells of lymphatic glands is well illustrated also in conditions of *pigmentary infiltrations*. Pigments of various kinds, carried to the glands, are taken up by endothelial phagocytes of the sinuses, and afterwards by the cells of the reticulum, in which they may persist for an indefinite period of time, as is seen in tattooing. Here also the lymphocytes take no part in the process. In cases of *anthracosis* carbon particles are dealt with in a similar way and they come to form black masses which replace the lymphoid tissue ; as a rule there is comparatively little thickening of the stroma. In *silicosis,* on the other hand, marked fibrosis results from the irritation caused by stone particles, and the glands become enlarged and indurated. Where there has been local hæmorrhage an accumulation of blood pigment, especially of hæmosiderin, may be seen in the related lymphatic glands ; and a remarkable accumulation of hæmosiderin is met with in certain of the abdominal glands in *hæmochromatosis* (p. 166). Sometimes the amount is so great that the structure of the gland is quite obscured by the masses of pigment, and we have found that the iron may constitute more than 10 per cent. of the dried substance of the glands. In such cases there is no evidence that excessive blood destruction is present.

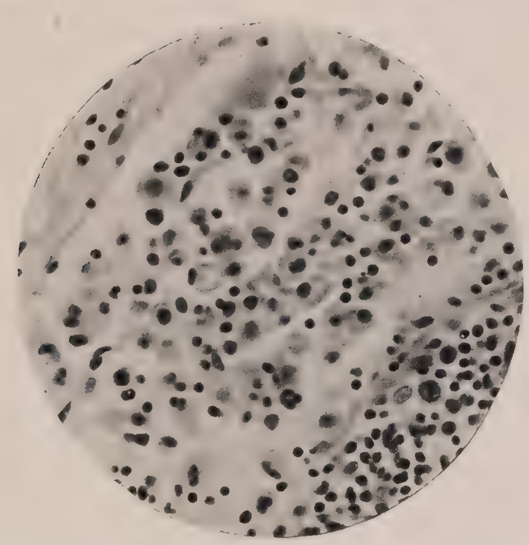

Fig. 315.—Section of Lymphatic Gland in Typhoid Fever, showing Lymph Sinus packed with Macrophages, some of which contain ingested remains of cells ; lymphoid tissue to lower right of field. × 350.

Glandular fever. This disease, which is apparently a specific infection, occurs in small epidemics and affects chiefly children and young subjects. It is characterised by swelling and tenderness of lymph glands, fever lasting a week or two and increase of non-granular cells in the blood. The anterior cervical glands are usually those first affected, but other groups may be involved ; some degree of splenic enlargement is not uncommon. The disease is rarely fatal. At first there may be an ordinary leucocytosis, but soon the characteristic blood picture appears, namely, a moderate rise in the leucocyte count with a high proportion (sometimes over 50 per cent.) of non-granular cells. These cells have been described as lymphocytes, abnormal mononuclears or simply as mononuclears. Apparently variations are met with, but usually most of the cells seem to be of the lymphocyte class. The lymphatic glands show a general hyperplasia with increased mitoses of lymphocytes, swelling of endothelial cells and excess of lymphocytes in the sinuses. The changes described point to the condition of the blood being the result of increased production of lymphocytes in the lymphoid tissues. The disease is known also as *infectious mononucleosis*.

Chronic Enlargement of Lymphatic Glands occurs in a variety of conditions, and is, of course, a very important clinical sign. At one end of the series may be placed chronic infections, at the other end tumours, whilst as intermediate conditions there are certain systemic diseases of the glands, the real nature of which is unknown. In the absence of knowledge of etiology it is not possible to draw sharp distinctions, but we may conveniently classify the main types of enlargement, thus :—

(1) Chronic infections, especially tuberculosis ; also syphilis.
(2) Lymphadenoma or Hodgkin's disease.
(3) Leukæmia and pseudo-leukæmia.
(4) Tumour growth, primary and secondary.

Local glandular enlargement may, of course, occur secondarily to an inflammatory condition in some part—for example, enlargement of the cervical glands in septic conditions of the mouth and fauces ; and this fact must be kept in view in the investigation of any case with a view to diagnosis. So also in relation to ulcerated tumours, enlargement of the lymphatic glands may be of inflammatory nature and not necessarily due to secondary growth.

(1) Chronic Infections

(A) **Tuberculosis.** Tuberculous disease of lymphatic glands is a very common lesion and may produce serious effects. The affection appears first in the group of glands in relation to the site of entry of the bacilli ; thus the cervical, bronchial, and mesenteric groups are the commonest to be involved. From the group of glands first infected the disease may spread to others. Infection of the bronchial glands is nearly always due to lesions in the lungs ; much less frequently due to spread downwards from the cervical glands. The tuberculous lesions, which may be either of slight degree or extensive, are of two main types—the commoner one being of *caseating*, the other of *proliferative* type.

In the *caseating type* the tubercles become conglomerate and then undergo extensive caseation, and so the process spreads till ultimately the whole gland is destroyed. Glands affected in this way undergo great enlargement and form large irregular masses with matting between. We have already referred to the regular occurrence of caseating tubercle in the tracheo-bronchial glands in relation to the pulmonary lesions in children and its absence in the chronic phthisis of the adult (p. 417).

Such a caseous lesion, formerly known as *scrofula*, is common in the cervical glands. They may become adherent to the skin and lead to ulceration, with discharge of the softened caseous material and then infection with pyogenic organisms may occur. Small sinuses thus formed may go on discharging for a long time; they may heal up and break down again, and the irregular cicatrices resulting may give rise to considerable disfigurement. Such results are now, however, usually avoided by operation. In certain cases, the disease passes into a quiescent condition; the caseous material not infrequently undergoes calcification, whilst great thickening of the surrounding capsule occurs. In children, tuberculosis of the mesenteric glands, the result of infection from the bowel, may give rise to great swelling and diffuse caseation, the condition being known as *tabes mesenterica* (p. 564). It is not uncommon to find at post-mortem examinations on adults the lower mesenteric glands transformed in this way into hard cretaceous masses, which represent a healed tuberculosis of intestinal origin.

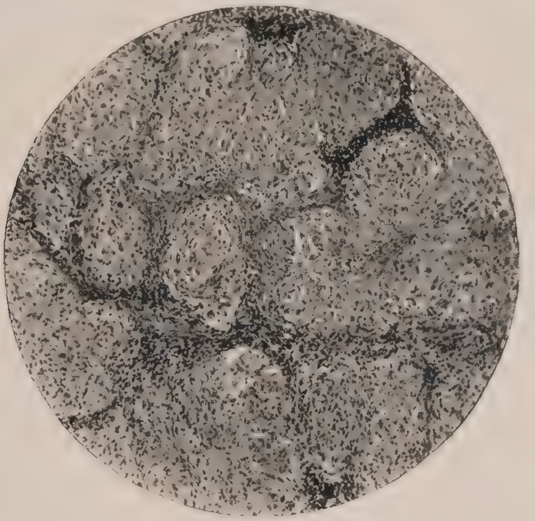

Fig. 316.—Proliferative and Non-caseating type of Tuberculosis in Lymphatic Gland.

Note the tubercle follicles without giant-cells and without caseation. (D. F. C.) × 75.

In the *formative* or *proliferative* type of tuberculosis also there is much enlargement of glands, which come to have a greyish or somewhat pinkish appearance, and the condition may readily be mistaken for lymphadenoma. On microscopic examination, the gland substance is seen to be largely replaced by a comparatively cellular tissue in which the predominating cell is of the endothelioid type (Fig. 316). Giant-cell systems may or may not be prominent, but there is little or no caseation or necrotic change. It is not possible to explain the remarkably different characters of tuberculous lesions of lymphatic glands. It may be that the proliferative type is met with when the tissues are little susceptible to the toxins of the bacilli, or, on the other hand, as has been suggested by some writers, this variety of tuberculous lesion may be caused by bacilli of attenuated virulence, so that there is little necrotic action. So far as we know, however, differences in the type of bacilli in the two conditions have not been demonstrated.

(B) **Syphilis.** Enlargement with induration of the regional glands in relation to the primary sore, has already been described, and the importance of lymphatic spread of the spirochætes has been emphasised (p. 103). The enlargement gradually subsides, but some induration may persist for a considerable time. In the secondary stage, there is often general glandular enlargement, though certain glands are specially prone to be affected. It is related to the general dissemination of the spirochætes in the skin lesions and is often attended by a certain amount of pyrexia. The enlargement is moderate or slight, and gradually passes off, but some glands may remain in an indurated state. In the tertiary stage, localised lesions in the form of necrotic inflammation and gumma are sometimes met with. Gumma is comparatively rare, but may reach a considerable size; we have seen one of about the size of a hen's egg. The lesion tends to undergo fibrosis and contraction rather than softening.

(2) Lymphadenoma or Hodgkin's Disease

This affection is characterised by a progressive and usually painless enlargement of lymphatic glands and other lymphoid tissues; there may be also nodular and more diffuse formation of new tissue in various organs. It is usually a chronic disease lasting two or three years and is attended by anæmia and a certain degree of pyrexia; it practically always leads to a fatal result. In some cases it runs a relatively acute course of a few months. We may state that the description now given by writers is essentially the same as that first given by Greenfield many years ago. It is well that this fact should be mentioned, as it is generally overlooked by writers on the subject.

Lymphadenoma usually starts first in the cervical glands and spreads to other groups, but in a fair proportion of cases the retroperitoneal glands are first involved, and from these there is extension to the mesenteric glands, inguinal glands, etc. (Fig. 317). It is said to begin occasionally within the thorax, but such an occurrence is very rare. The enlarged glands are at first moderately soft and succulent and of uniform greyish or pale pink colour, but, as the enlargement progresses, they become denser in consistence, and may come to form large masses which produce important results by pressure, e.g. on the trachea, veins, etc. Ultimately they may be densely fibrosed, and may show yellowish areas due to necrosis, but there is no suppuration and no real caseation; there is usually little or no matting of the glands.

In the *spleen* a similar change extends to the Malpighian bodies. These become enlarged and changed into masses of tissue of whitish or yellowish colour, which are of various shapes and scattered throughout the pulp ; thus a characteristic appearance is produced, which has been compared to portions of suet in a German sausage (Fig 318). The affection of the Malpighian bodies may occur throughout the spleen, or it may be in patches, and some of the nodules may reach a considerable size. There is also a general hyperplasia of the pulp, so that the organ as a whole may be much increased in size, the weight sometimes being over two pounds. In some cases there is merely a general enlargement without the characteristic lesion in the Malpighian bodies, and in others again the organ may be little altered. Nodules of newly formed tissue may occur in other organs, especially in the liver and kidneys (Fig. 319), and in the former there may be diffuse growth along the portal tracts. In the lungs also, lesions both of a focal and diffuse character occasionally occur, especially when the bronchial glands are affected. Lesions in the form of firm plaques, which may ulcerate, sometimes are met with in the intestines, and we have seen a similar condition in the stomach. There is generally some extension of the red marrow in the long bones, with both a leucoblastic and an erythroblastic reaction. Nodules of the characteristic tissue are sometimes met with in the bone-marrow. It is thus seen that while the lesions are mainly in lymphoid tissue, they are met with in various organs. We may mention that we have seen nodules of characteristic structure on the diaphragm and even in the spinal dura with resulting pressure on the spinal cord and paraplegia. Further, while the lesions in the organs are mainly of the type of diffuse growth and small nodules, cases are occasionally met with in which tumour-like masses of considerable size and relatively cellular character are present (Fig. 319). The distribution of the changes described varies greatly, and while the glandular involvement is often widespread it may, on the other hand, be relatively limited. We have seen one case in which the spleen alone was affected.

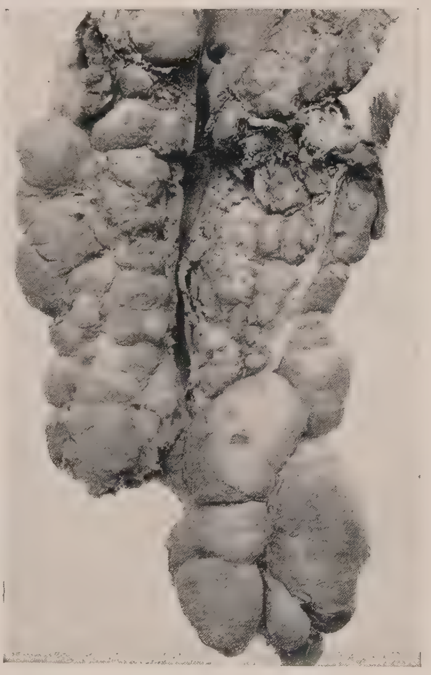

Fig. 317.—Mass of Retro-peritoneal Glands from a case of Lymphadenoma.

The aorta is seen slit up from behind and is surrounded by the masses of glands. × $\frac{2}{3}$.

Anœmia of microcytic type is usually present and sometimes reaches a marked degree. In the great majority of cases in the adult, there is fairly well-marked leucocytosis of the ordinary type, the proportion of polymorphonuclears being increased. An increase of the lymphocytes is sometimes met with in the earlier years of life, but it is rare in the adult. Eosinophilia has been recorded in some cases, and such an occurrence is of interest in relation to the local eosinophilia in the lesions; but, as a rule, there is no increase of eosinophiles in the blood. None of the changes characteristic of leukæmia are met with in Hodgkin's disease, and, as we shall see, the lesions are essentially due to changes in the stroma, not in the leucocytes. It may be added that amyloid disease has occasionally been observed in lymphadenoma.

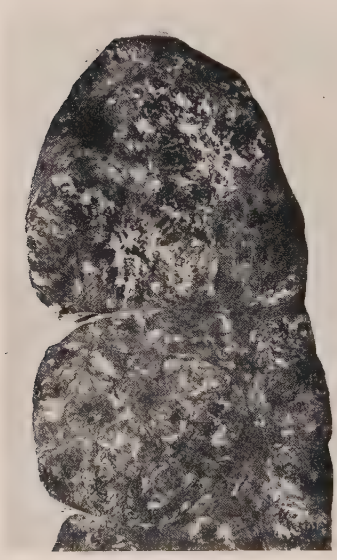

FIG. 318.—Section of Spleen in Lymphadenoma, showing the characteristic affection of Malpighian Bodies. × $\frac{2}{3}$.

As has been said, irregular pyrexia is of common occurrence, but in some cases it may assume a definite character known as the Pel-Ebstein type. In this there are periods of pyrexia of a week or more, separated by remissions of two or three weeks. The pyrexia

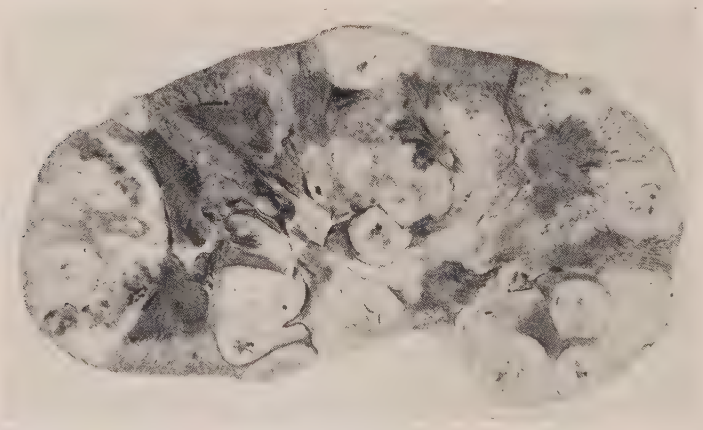

FIG. 319.—Nodules of Lymphadenoma in Kidney.

The growth was unusually extensive and the cells were of aberrant type. × $\frac{2}{3}$.

has no relation to the extent of the lesions and its cause is unknown.

Microscopic Examination at an early stage shows that there is proliferation of the endothelial cells and the cells of the reticulum, which produce a cellular tissue of somewhat characteristic appearance. The cells of this tissue vary considerably in form, are rounded, oval, or tailed, and contain a rather pale nucleus of the vesicular type, with definite nuclear membrane and containing granules of chromatin. Some of these cells increase in size and come to contain several nuclei or a large convoluted or ring-shaped nucleus (Fig. 320). Scattered amongst these cells are lymphocytes in varying proportion, apparently survivors from the lymphoid tissue, and not infrequently the tissue is overrun with numerous eosinophiles. The evidence is in favour of the view that these are not formed locally but emigrate from the blood vessels, and we have seen in one or two instances distinct increase of eosinophiles within the capillaries of the glands. Sometimes, however, there are practically no eosinophiles in the newly formed tissue, and it would appear as if the chemotactic agent acting on these cells were present only in certain cases, and in these probably only at certain times.

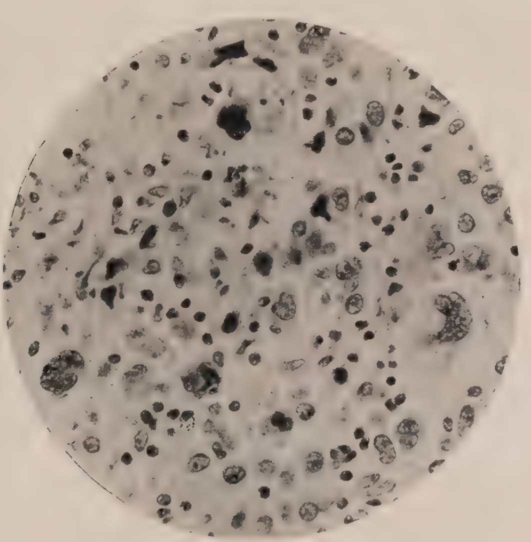

Fig. 320.—Lymphadenoma in Lymphatic Gland at a comparatively early stage, showing the typical structure.

Note the large cells with irregular and convoluted nuclei. × 500.

The newly formed cellular tissue at first occurs in patches, but soon extends through the gland substance, replacing the lymphoid tissue and destroying the architectural structure. At first fine fibres of reticulum are present between the cells, but soon collagen fibres appear, and a condition of fibrosis may follow. Ultimately the gland substance may be largely replaced by dense hyaline connective tissue in which there are surviving collections of lymphocytes, and necrosis may occur in parts. It is to be noted that, while in most cases lymphadenoma is essentially a chronic disease, there are relatively acute cases in which the glandular enlargement occurs rapidly but is more restricted, while the tissue presents a greater proportion of aberrant cells ; in fact the appearance may resemble that of a mixed-cell sarcoma. In these cases there is often a rapidly advancing anæmia.

The lesions in other organs are of the same nature as in the lymphatic glands. In the Malpighian bodies of the spleen, for example, there is a proliferation of endothelial and reticulum cells, and the change may be wonderfully uniform ; it tends to encroach upon the pulp at the periphery, and blood pigment derived from included red corpuscles may be present. The cellular proliferation is followed by thickening of the stroma, which usually begins at the margin, and ultimately much fibrosis occurs, while there may be a considerable degree of hyaline change in the vessels. We thus have a picture of the affection becoming generalised in various organs, while the histological changes are remarkably uniform.

As to the true nature of lymphadenoma no definite statement can be made. It is manifestly either a chronic infective process or a malignant neoplasm. The general changes correspond rather to a reactive process ; the lesion seems to extend by the other cells of the tissue taking part in the proliferation, rather than by an infiltration of cells already possessing malignant properties. Also the way in which fibrosis regularly follows the proliferation, resembles what is seen in an infective granuloma. The pyrexia which may be a prominent feature, points in the same direction. On the other hand, no definite organism has been demonstrated in the lesions, and it has not been found possible so far to transmit the disease to any of the lower animals.

The cellularity of the growth and the aberration in cell types met with in certain acute cases have led to the view that a sarcomatous change is occasionally superadded. Ewing, for example, speaks of ‘ Hodgkin's granuloma ’ and ‘ Hodgkin's sarcoma.’ It must be admitted that in some cases the histological appearances cannot be distinguished from those of sarcoma, and the cells can be seen invading blood vessels after the manner of a malignant growth ; but, in our experience, all degrees of cellularity can be present in the same case and it does not seem possible to distinguish two distinct types of tissue—a granulomatous and a sarcomatous. The question is, however, an open one. Though sometimes of very chronic character, the disease is probably always progressive and leads to a fatal result.

Detailed investigations carried out by the workers of the Rose

Research on Lymphadenoma[1] have failed to reveal the presence of any parasite in the tissues. It was found, however, that the affected glands contain a pathogenic agent which, when injected into the brain of a rabbit, produces an encephalitic condition with definite symptoms. After an incubation period of two or more days nervous symptoms develop, of which the most important are inco-ordination and ataxia accompanied by rigidity of muscles and spastic gait; death usually follows. It has been shown that this method, now known as Gordon's test, is of great diagnostic value. A positive result is nearly always obtained with lymphadenoma tissue, though it may be absent in some cases especially those of very chronic character, or at a very early stage. On the other hand, it is scarcely ever given by tissue from other human lesions. These results suggest that the disease is due to a filter-passing organism, but this has not been proved. It may be added that the characteristic lesions of lymphadenoma have not been experimentally reproduced in any animal.

Friedemann has shown that in normal red marrow and occasionally in the spleen of some species of animals, an agent is present which has an effect closely similar to that described when injected into the brain of a rabbit; he considers it a proteolytic enzyme. The evidence obtained goes to show, however, that this is not the same as the agent in lymphadenoma and his results do not affect the validity of the test in the latter.

(3) Leukæmia and Pseudo-leukæmia

Marked enlargements of lymphatic glands which occur in lymphatic leukæmia, have already been described in connection with the account of this disease (p. 480); and diagnosis will be readily made from an examination of the blood. Cases are met with, however, where there is a similar painless enlargement of lymphatic glands and other lymphoid tissues, without the presence of a leukæmic condition of the blood. The enlargement may be due entirely to accumulations of lymphocytes, and the structure resembles that found in lymphatic leukæmia. When this is the case, the term pseudoleukæmia may be applied. It is interesting to note that in some such cases there is a relative lymphocytosis without increase in the total number of leucocytes, and that later the changes characteristic of lymphatic leukæmia appear in the blood. It would therefore seem that the essential morbid change may be present in the lymphoid tissues for some time before leukæmia appears. In one case observed by us the leukæmic state developed several years after the lesion in the lymphatic glands. Pseudo-leukæmia may thus be regarded as of the same nature as lymphatic leukæmia, and is sometimes observed as an 'aleukæmic stage' of the latter. An aleukæmic stage is sometimes observed also in the myeloid and monocytic types. In such conditions examination of the marrow by sternal puncture has been found of service.

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[1] *Rose Research on Lymphadenoma*, Bristol, 1932.

(4) Tumours

The primary tumours, simple lymphoma and lymphosarcoma, have been already described (p. 254). The commonest sites of the latter are the mediastinal glands, mesenteric glands, and cervical glands. The growths are often of multiple origin but there is also a tendency to spread by the lymphatics and to involve the neighbouring glands. In these ways, large conglomerate masses of glands result and the growth may extend to the tissues around. As already stated, however, there is a large group of hyperplasias and malignant growths affecting lymphatic glands which have not yet been satisfactorily differentiated. The latter are both of the type of sarcoma and endothelioma. In addition to the round cell lymphosarcoma there are also types where the cells are angular or of spindle shape and occasionally a reticulosarcoma may be composed of large cells with a tendency to aberrant form, there being a delicate reticulum between the cells (Fig. 321). There is also the markedly polymorphous growth already referred to, to which the term 'Hodgkin's sarcoma' has been applied. In all these conditions there is multiple affection of glands. Endothelioma is of occasional occurrence (Fig. 167).

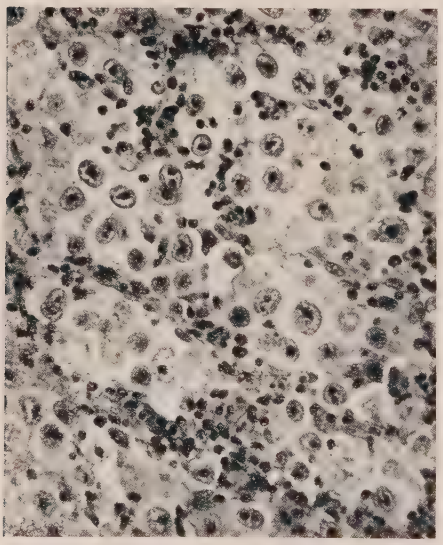

FIG. 321.—Reticulo-sarcoma of lymph gland, showing large rounded cells with lymphocytes between. (J. S. F. N.) × 300.

Lymphangioma (p. 218) in connection with the lymphatic vessels is a not infrequent simple growth.

Secondary growths have been sufficiently dealt with in the chapter on tumours; they are common in all varieties of carcinoma with the exception of rodent ulcer, and also in melanotic growths. It may be well to recall and emphasise the wide spread by the lymphatics which may take place, and the involvement of distant glands—for example, the supra-clavicular glands in cases of gastric carcinoma.

BONE-MARROW

Introductory. As has already been stated (p. 434), the bone-marrow is the formative tissue for most of the cells of the blood, namely, the leucocytes of the granular series, the red corpuscles and also the platelets ; and there is no evidence that any of these are normally formed in the adult in any other part of the body. In the adult the red hæmopoietic marrow is restricted to the ribs, vertebræ and sternum and to the ends of long bones, and there it is mixed with a certain proportion of fat. Accordingly, increase of the marrow in response to requirements can occur by displacement of the fat in the small bones as well as by extension of the red marrow into the shafts of the long bones ; these two changes usually take place together. The manner in which the marrow responds to increased call for cells (leucocytes, and red corpuscles) has been described in connection with inflammation and diseases of the blood, and we shall here summarise only some of the main facts. It is to be noted, however, that in the child the medullary cavities of the long bones are occupied by red marrow. Fatty marrow visible to the naked eye appears in the lower end of the femur about the seventh year of life and then gradually increases in an upward direction. The marrow of this bone becomes entirely fatty at the age of twenty-one or shortly thereafter. Variations, however, are common. Hyperplasia of red marrow in the femur occurs first in the upper end of the diaphysis and extends downwards.

In all obscure blood conditions the examination of the bone-marrow by sternal puncture has been found to be of great service.

Besides undergoing hyperplastic or formative reactions, it is to be noted that in conditions of disease, the marrow, like any other tissue, may be damaged by toxins or suffer from impaired nutrition, and thus may become altered in character. Further, while the marrow as a hæmopoietic tissue is quite distinct from the bone which encloses it, the two tissues may suffer together in infections. For example, in tuberculosis and in pyogenic diseases, both are invaded and destroyed. The same holds in the case of secondary growths of cancer, and the marrow seems a specially favourable nidus for the settling of cancer cells and their subsequent growth.

The various changes in the bone-marrow may be conveniently considered under the following headings, viz. :—

(1) *Reactive hyperplasia.*
(2) *Nutritional disturbances.*
(3) *Inflammatory conditions.*
(4) *Neoplastic conditions.*

As most of the changes have been dealt with in other chapters, only a brief survey need be given.

(1) **Reactive Hyperplasia.** As has been previously stated, this is of two main types, namely, the *leucoblastic* and the *erythroblastic.*

The hyperplasia is shown by an increased proportion of red marrow in the cancellæ of the small bones and by a replacement of the fatty marrow of the long bones by red marrow; this replacement, in the case of the femur, starting at the upper end and extending downwards. In this newly formed marrow all the constituents are present but there is an excess of myelocytes or of erythroblasts according to the nature of the reaction. New foci of myeloid tissue may appear not only in the fatty marrow but also occasionally in other organs—spleen, liver, etc. (p. 442).

An important fact now recognised is that in conditions of disease there may be marrow hyperplasia, both erythroblastic and leukoblastic, whilst the delivery of the final products to the blood is deficient. Thus there may be erythroblastic reaction in conditions of anæmia, e.g. simple microcytic anæmia and splenic anæmia, whilst the number of reticulocytes in the blood is below normal. So also in many cases of agranulocytosis the myelocytes may be abundant, whilst the polymorpho-nuclear leucocytes are scanty, both in the marrow and in the blood. In other words, there may be hyperplasia with deficient or arrested development. This is of importance in interpreting the condition of the marrow.

(*a*) *Leucoblastic Reaction.* It has now been established that this may be of different kinds. In ordinary leucocytosis such as that in pneumonia, suppurative conditions, etc., the increase is on the part of the finely granular neutrophile myelocytes, and these cells, many of which can be seen to be in active mitosis, form a larger proportion of the marrow. The principles on which these changes are brought about have already been discussed (p. 77). On the other hand, when red marrow is being formed anew in fatty marrow myelocytes are formed from myeloblasts and these in their turn from reticulo-endothelium. In *eosinophilia*, notably in the case of nematode infections, there has been found an increase of eosinophile myelocytes, and increased multiplication of these cells. No corresponding reaction is known in the case of the basophile myelocytes, and this may be taken as being in accordance with the fact that there is no definite condition known in which a basophile leucocytosis occurs in the blood. In fact, we have no satisfactory knowledge as to response on the part of these cells to chemotactic substances. In typhoid fever an increase of non-granular cells has been found in the marrow, but this has been interpreted in different ways, some regarding them as cells of the lymphoid series, and others as promyelocytes or myeloblasts.

The leucoblastic reaction, which normally occurs, may fail on account of the defective resisting powers of the individual. There may then be leucopenia instead of leucocytosis. This has already been considered (p. 80).

(*b*) *Erythroblastic Reaction.* This is of two main types, the *normoblastic* and the *megaloblastic*. The former, characterised by active proliferation of the ordinary erythroblasts which come to constitute an increased proportion of the cells of the marrow, may be regarded as the normal response to increased demand for red corpuscles. Thus it is seen after hæmorrhage, and after blood destruction of various kinds. It is also a noteworthy occurrence as a result of diminished oxygen tension when a person lives at a high altitude (p. 434). The megaloblastic change, which represents an earlier or more embryonic type of blood formation, occurs especially in pernicious anæmia, but also in other forms of megalocytic anæmia (p. 460). It is rare in other conditions in the adult.

Phagocytosis is seen in the bone-marrow, both in infections and in cases of blood destruction. Thus red corpuscles may be found in the interior of the macrophages and deposits of hæmosiderin may occur, but, on the whole, the marrow plays a less important part than the spleen in destructive processes and in phagocytosis. As in the spleen and lymphatic glands, the macrophages are derived mainly from reticulum and endothelial cells. The storage function of the marrow is indicated by the accumulation of lipoids which occurs in Gaucher's disease and allied conditions (p. 499).

Aplasia. This term is applied when there is deficiency of hæmopoietic marrow. An extreme condition is that in which very little red marrow is present, the cancellæ even of the short bones being largely occupied by fat. Such a state in its extreme form is occasionally met with in early life, but it is very rare ; it may result in an advancing and fatal anæmia—*aplastic anœmia* (p. 468). In some rare cases of pernicious anæmia, the red marrow does not undergo the usual increase, whilst in others it is in an aplastic state (p. 455). Cases of this kind usually run a rapid course. The causation of aplasia is not fully understood. In some extreme cases it may represent a *congenital* or *primary* deficiency, but it is often *secondary* to toxic effects of various kinds. Poisons such as saponin, benzole, ricin, lead, etc., which cause anæmia, have been shown to injure the marrow and lead to a diminution of its cells, and it is well recognised that the rays of radio-active substances and X-rays have an important influence in damaging the marrow and thus leading to anæmia. An interesting example is the anæmia occurring in dial-painters, the luminous paint which is used containing radium and mesothorium. These metals are stored in bone and injure the marrow, producing a condition of anæmia, which may be of the megalocytic type. The injury inflicted on the marrow by such chemical and physical agencies may be slight and merely interfere with the output of cells ; or, on the other hand, may be more severe and implicate the stem cells, thus leading to an aplastic state. The degree and rapidity of recovery after damage has been inflicted of course vary greatly. It is also believed by some that aplastic changes may result from exhaustion of the marrow following hyperplasia.

(2) **Nutritional Disturbances.** The bone-marrow may be injured by toxins, as explained above, and it suffers also in states of mal-

nutrition. In cases of wasting disease—carcinoma, chronic Bright's disease, etc.—the fat of the yellow marrow of long bones becomes absorbed, and a sort of gelatinous tissue of brownish tint takes the place of the adipose tissue (Fig. 322). This gelatinous material may replace some of the red marrow in the small bones. Thus the marrow of long bones in disease may be of the ordinary fatty type, the gelatinous type, or the red hæmopoietic type; and any two of these, or in fact all three, may be present together. In cases of cancer, for example, the fatty marrow may in part have become replaced by red marrow, and in part have undergone gelatinous degeneration. We may add that a certain amount of gelatinous change may occur merely as an ordinary senile phenomenon. As has been mentioned above aplasia is often a nutritional disturbance due to toxic action; it is sometimes associated with an appearance of gelatinous marrow. When recovery occurs, regeneration of the cells may follow, but this may take place slowly.

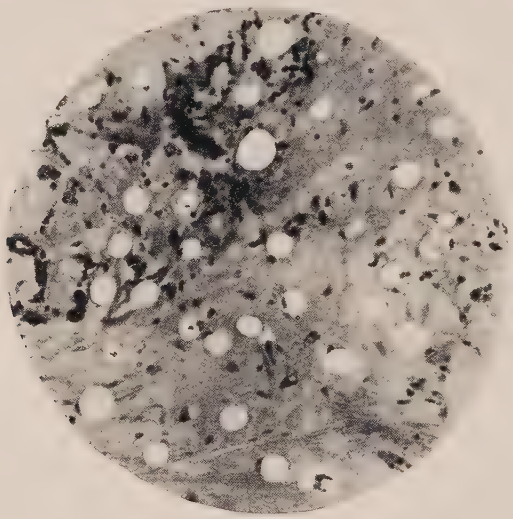

Fig. 322.—Marrow of Femur in a case of Carcinoma, showing Gelatinous Degeneration.

Note clumps of surviving marrow cells and also some wasted fat cells in a homogeneous matrix. × 300.

In very severe infections, evidence of damage may be present; some of the myelocytes may show degenerative or necrotic change with chromatorrhexis, and sometimes there may be even focal necrosis. The latter is met with especially in smallpox. Hæmorrhages may be present in the marrow in infections, such as bacterial endocarditis, typhoid, etc., and also in anæmia, scurvy, phosphorus poisoning, etc. They may result either from toxic action or from the actual presence of organisms. In infantile scurvy, in addition to the occurrence of hæmorrhages, the cells of the marrow may become replaced to a considerable extent by a fibro-cellular connective tissue. Various other changes occur in association with diseases of the bones (*q.v.*).

(3) **Inflammatory Changes.** The bone-marrow may be invaded by organisms of various kinds, and both acute and chronic inflammatory conditions result. Of the former, the most important is acute suppurative osteomyelitis, and of the latter, tuberculosis. Both of these, which are hæmatogenous infections, are described in connection with disease of the bones (pp. 810, 814). In acute miliary tuberculosis numerous small tubercles may be present in the marrow. Gumma of the marrow has been described, but it is very rare.

(4) **Neoplastic Conditions.** Malignant neoplasia in the marrow may be, (*a*) diffuse in character as in leukæmia, or (*b*) in the form of nodular masses of growth. In myeloid chloroma, however, we have an example of discrete growths which are associated with leukæmia. Another malignant growth which possesses features of interest arises from the marrow cells and is not associated with a leukæmic condition of the blood. This is the myeloma.

Myeloma. This is a round-cell growth, and is not to be confounded with the myeloid sarcoma (p. 231). The myeloma usually occurs in the form of numerous nodules which are met with especially in the bones normally containing red marrow (Fig. 323), although they occur in the long bones also. Extramedullary growths have been described in rare cases. The nodules lead to expansion and absorption of the bones, and spontaneous fractures are of common occurrence. The ribs, for example, may be so extensively involved as to be quite fragile and easily broken (Fig. 324). In the great majority of cases, a form of protein (often known as Bence-Jones protein) is present in the urine, but this is not peculiar to myeloma.

The Bence-Jones protein was at first considered to be an albumose, but it differs from the latter in certain respects ; for example, its molecule is of larger size and it is non-dialysable. It coagulates at a relatively low temperature and the precipitate disappears on boiling and reappears on cooling. The precipitate with nitric acid and other reagents behaves in a similar way. The protein is met with in the urine in other diseases where bones are involved, for example, in cancerous invasion of bone, leukæmia and chloroma. But whilst it occurs especially when the marrow is implicated it has occasionally been observed in other conditions. The protein has not been found in normal marrow and its mode of origin is not definitely known. According to Wells it is related to the water-soluble globulin of the blood. A point of interest is that when injected into rabbits it gives rise to a precipitin which reacts with human serum, this indicating that it has the essential constitution of a human protein.

In myeloma, it appears that the multiple tumours are to be regarded as independent growths, the result of a system disease of the marrow rather than as metastatic in nature. The histological structure of myeloma varies considerably, and different types have been distinguished. The cells are of rounded form and often somewhat undifferentiated, but, in most cases, they resemble myeloblasts (Fig. 325), and sometimes contain neutrophile granulations or even eosinophile granulations, the latter occasionally varying much in size. But although the origin from cells of the myelocyte series appears in many cases fairly clear, it is a striking fact that myeloma is not attended by the features of myeloid leukæmia. In some cases, the cells appear to be lymphoidal in nature, and in fact may present a close resemblance to plasma cells—a malignant plasmacytoma. This variety, which is less common, is sometimes attended by similar growths in the lymphatic glands. It is a fact of some importance that plasmacytoma is occasionally met with as a solitary growth of bone, leading to rarefaction and sometimes to spontaneous fracture, and that cure has been effected by surgical removal, there being no recurrence. A similar type of growth composed of plasma cells occurs also in the soft tissues, particularly in the naso-pharynx. These growths are radio-sensitive. In one or two cases the cells of a myeloma have been found to be erythroblasts—erythroblastoma.

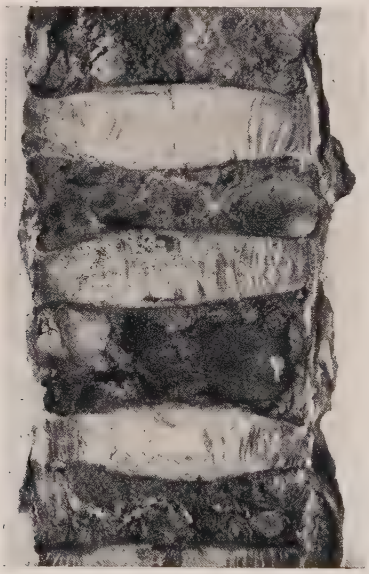

Fig. 323.—Multiple Nodules of Myeloma in Vertebral Column.

Note the collapse of the vertebræ with shortening.

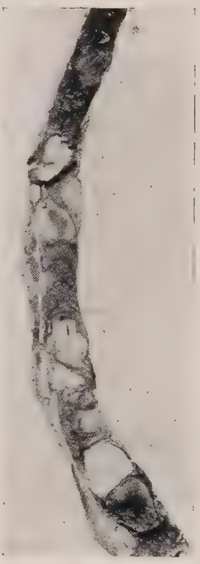

Fig. 324.—Multiple Nodules of Myeloma in a Rib; numerous spontaneous fractures were present.

Another rare form of growth is the myeloid chloroma (p. 482), a cellular tumour of green colour which occurs in connection with bones, and apparently originates from myeloblasts. It is associated with acute myeloid leukæmia (p. 482). It is not known why leukæmia should occur with chloroma and not with myeloma.

In rare instances *simple tumours* occur in the marrow, but these take origin from the connective tissue and not from the cells proper to the marrow; fibroma, myxoma, and angioma are examples.

Secondary growths, both of carcinoma and sarcoma, are fairly common in the bone-marrow; and in the case of melanotic growths and cancers of certain organs, especially the mamma, prostate, and thyroid, the nodules may be very numerous and widespread. They occur especially in the red marrow. These growths are described in connection with disease of the bones. When the marrow of various bones is extensively invaded, there is often to be seen a compensatory formation of red marrow in the long bones. The changes which occur in the blood are described on p. 469. Further, in some cases of carcinoma, especially of the prostate, there may be a remarkable condition of overgrowth and sclerosis of the bone around the nodules, and the bone-marrow may be greatly encroached upon by the condensation of the bone with resulting anæmia, often called *osteosclerotic anæmia.* The effect corresponds with that seen in the marble-bone disease of Albers-Schönberg. Myeloid tissue may be found in the liver and spleen, and a compensatory blood formation may thus occur in these organs.

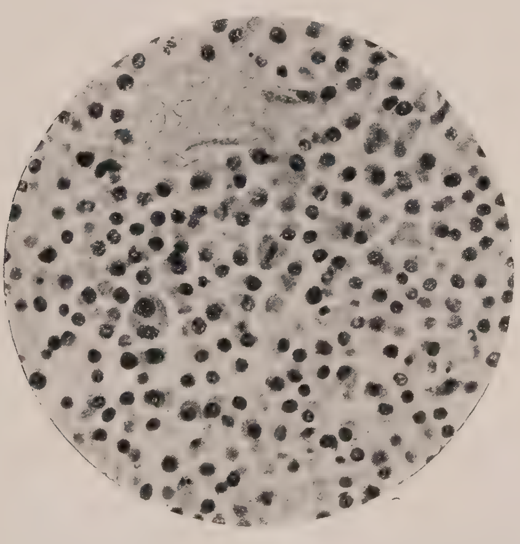

Fig. 325.—Section of Myeloma, showing a uniformly cellular tissue, the round cells being of myeloblastic type. × 500.

CHAPTER XIII

ALIMENTARY SYSTEM

ŒSOPHAGUS

Inflammatory Changes. The œsophagus is the part of the alimentary canal which is least frequently the seat of inflammatory change. Lined by squamous epithelium and adapted to bear without injury the rapid passing of food over its surface, it has marked powers of resistance and is comparatively seldom the seat of primary bacterial invasion. Acute catarrhal and even pseudo-membranous inflammations have been described in connection with various infective fevers, but they are relatively rare; the extension of the lesions of diphtheria from the fauces to the upper part of the œsophagus may be mentioned as an exceptional occurrence.

Phlegmonous inflammation is due to the entrance of pyogenic organisms into the mucous and submucous coats, and may sometimes spread widely. It may result from spread of suppuration from the fauces or from other neighbouring parts, e.g. from the larynx affected by suppurative perichondritis. It may develop in connection with an ulcerating carcinoma or may be set up by an impacted foreign body. Inflammatory change is not infrequently caused by the swallowing of hot or irritating fluids, and severer degrees are met with in the case of caustic substances. The latter produce effects according to their nature and concentration. When concentrated, they produce necrosis in varying degree; when more dilute, the result is rather of an inflammatory nature. The caustic effect is most marked on the summits of the longitudinal folds, but in severe cases it may extend deeply and a considerable part of the wall may be destroyed. In cases where recovery occurs, the dead material is gradually separated and ulceration follows, which may be of chronic nature, and ultimately stenosis may result. The effects of the various caustics correspond with those in the stomach (p. 532).

Chronic catarrh is favoured, as elsewhere, by the presence of passive congestion. It is common in alcoholism, and there is often opacity along the summits of the longitudinal folds. Circumscribed patches of thickening and opacity, known as *leukoplakia*, occur in the same conditions, but the causation is often obscure. They consist mainly of thickened epithelium.

The term *œsophagitis dissecans superficialis* has been applied to a very rare condition in which the whole of the superficial layer of the œsophagus becomes separated and discharged as a cast of the tube. The presence of signs of inflammatory change such as round-cell infiltration, or even a purulent layer, has been noted underneath the separated epithelium in some cases, hence the term applied to it. In a case which we examined, however, there was no evidence of inflammation and no noteworthy change in the separated epithelial layer; separation of the epithelium had occurred on various occasions, and on each was accompanied by great pain and discomfort until the cast was completely separated. The etiology of the condition was quite obscure. Occasionally large areas of superficial epithelium may be discharged after injury by scalding fluids, chemical irritants, etc.—this, of course, is of quite a different nature.

Specific Chronic Inflammations. All these are of very rare occurrence. Small *tuberculous* ulcers may be occasionally met with in the œsophagus in pulmonary phthisis as a result of swallowing sputum. Occasionally also the wall of the tube may be infected secondarily from a caseous lymphatic gland which has become adherent to it. *Syphilitic* lesions likewise are uncommon, although the occurrence of a gummatous infiltration in the wall of the tube has been observed. Sometimes in *actinomycosis* the infection starts from a lesion of the œsophagus, and in one or two instances this has resulted in connection with a grain impacted in the wall.

It may be added that *thrush* may occur in the œsophagus, usually as an extension from the mouth and fauces. The lesions are in the form of irregularly raised patches of opaque whitish appearance, which are composed of swollen and sodden epithelium infiltrated by the septate mycelial threads and spores of the parasite—the *Oidium albicans*. The patches may occasionally attain some size and affect a considerable part of the wall of the tube.

Circulatory Disturbances. The most important change of this kind is that which occurs at the lower end of the tube in cases of portal congestion, most frequently the result of cirrhosis of the liver. The veins near the cardiac orifice of the stomach, and often for some distance above, become distinctly varicose and form projections; they occasionally become ulcerated and severe or even fatal hæmorrhage may result. Fatal bleeding may occur in other conditions. Sometimes an aneurysm of the aorta may rupture into the œsophagus, though this is relatively rare on account of the mobility of the tube. A foreign body, especially a fish bone, may be impacted transversely in the œsophagus and ulcerate through the wall; we have seen two cases in which perforation of the aorta was brought about in this way. Also a carcinoma of the œsophagus, especially of the soft necrotic variety, may ulcerate into the aorta or other large vessel.

Digestion of the Œsophagus. This is met with in two forms, one being a post-mortem and the other an ante-mortem occurrence. The former, which has been longer recognised, is associated with post-mortem digestion of the stomach; the mucous membrane of the lower part of the œsophagus, which is usually relaxed, is discoloured, softened or it may be shreddy. But, as pointed out by Pringle and Teacher, whose conclusions I can confirm, ante-mortem digestion is by no means uncommon. It is characterised during life by hæmatemesis and may lead to a fatal result by actual perforation of the tube. They have met with it especially in severe toxic and infective conditions, particularly after operation, and regard it as due to the passage of gastric contents with very acid reaction into the lower part of the œsophagus. The wall of the œsophagus in this region shows brownish discoloration and is in various stages of destruction; a perforation may be present or the wall may be more extensively destroyed so that there is a large aperture of communication with the tissues outside. When the contained fluid has entered a pleural sac, as is not infrequently the case, the pleural membrane may be the site of numerous hæmorrhages and show early inflammatory change. A feature of the condition is that there may be extensive digestion of the tube whilst the adjacent part of the stomach wall is practically unaffected. From the conditions present it may be possible to recognise the digestion as an ante-mortem occurrence, but sometimes this can only be determined by finding evidence of reaction in the tissues on microscopic examination.

Peptic ulcer of the same nature as that met with in the stomach occasionally occurs at the lower end of the œsophagus (p. 533).

Stenosis and Dilatation. Obstruction of the œsophagus may be *organic* or *functional.* The former may be produced by a tumour projecting into the lumen, rarely a simple growth, more frequently carcinoma; in a malignant case, the obstruction may become less marked owing to the disintegration of the growth, and thus a deceptive appearance of improvement may result. When the cancer is of the more slowly growing variety, marked stenosis of the tube may follow; and a similar effect may be the result of healing of an ulcerative lesion set up by a chemical irritant, occasionally by syphilis. Obstruction is often caused from outside, e.g. by an aneurysm or by a tumour at the root of the lung; it is at times the result of spasm at the lower end. In all these conditions, if the obstruction lasts for some time, the part of the tube above usually undergoes a certain amount of dilatation and its wall becomes hypertrophied. Variations in the lumen occur as *congenital* abnormalities; sometimes there is a general dilatation of the œsophagus, sometimes a local one, especially at the lower end. Stenosis also may occur as a congenital condition; it may be general or involve only one segment.

Functional Obstruction. There is an important form of dilatation of the œsophagus—*œsophagectasia*—due to muscular constriction. The condition is also known as *achalasia of the œsophagus* and *cardiospasm.* It develops usually in early adult life and leads to dysphagia with regurgitation of food; later there may be serious obstruction. The constriction is at the diaphragm and much dilatation of the œsophagus with muscular hypertrophy of its wall results. There has been discussion as to whether the constriction is due to spasm or to failure to relax (achalasia), but in either case there is nervous incoordination with relative overaction of the sympathetic. Recently resection of the sympathetic fibres has led to relief of the condition in a number of cases.

It may be recalled that dysphagia may occur from functional constriction at the upper end of the œsophagus in anæmic women (p. 462). It is now generally regarded as due to the spasm of the crico-pharyngeus portion of the inferior constrictor of the pharynx.

Diverticula. Local dilatations are sometimes met with in connection with the œsophagus, and of these there are two varieties, namely the *pulsion diverticulum* and the *traction diverticulum.* The former, as its name implies, is caused by forcible distension, especially during the act of swallowing. It is usually not noticeable till early adult life but the origin of the condition may depend on a congenital weakness or deficiency in the muscle. The diverticulum is between two portions of the inferior constrictor of the pharynx ; it is accordingly really *pharyngeal* although it is often spoken of as œsophageal. Once a diverticulum has formed, as may result from stretching of the deficiency in the wall by a bolus of food, it tends to increase in size. It becomes distended with food during deglutition and gradually extends in a downward direction behind the wall of the œsophagus ; ultimately there comes to be a permanent collection of food in it and the sac may reach a large size. Such a diverticulum is lined by mucous membrane supported by connective tissue, but its wall usually contains no muscle ; occasionally ulceration may take place in it. A diverticulum may also occur anteriorly and bulge between the trachea and the œsophagus ; but much more frequently the site is in the posterior wall at the junction of the pharynx and œsophagus.

The *traction diverticulum* of the œsophagus is usually produced by the contraction of connective tissue pulling the wall outwards. It is most frequently the result of a mass of tuberculous lymphatic glands becoming adherent to the wall of the tube, and in the cases which we have seen, the glands have been calcified. Occasionally an adherent mass of silicotic glands causes the condition. A pouch with sharp apex is the result, and this is stretched and increased both by the contraction of the connective tissue and by the movements of the œsophagus. The important point is that ulceration of the diverticulum may occur and may lead to perforation, and then the œsophageal contents may gain access to the tissues of the mediastinum and set up a gangrenous inflammation which may extend to the pleura and other parts.

Such are the usual characters of the diverticulum which gives rise to serious results, but there are rare cases where a local diverticulum opposite the bifurcation of the trachea is due to a congenital abnormality, arising in the same way as a communication between the œsophagus and trachea (p. 527), but of minor degree. The congenital nature is indicated by the fact that sometimes the pouch has been lined by columnar epithelium.

Tumours. Amongst the *simple growths,* lipoma, fibroma, and myoma occur, the last mentioned occasionally reaching a considerable size, but all of them are rare ; they tend to project into the lumen and have a polypoid form. Papilloma, which may appear in multiple form, is met with, but it also is uncommon. Cysts and rhabdomyoma may be mentioned as of rare occurrence and resulting from congenital abnormalities.

Of the *malignant growths,* carcinoma is by far the commonest and is comparatively frequent. It is met with in the later years of life, usually after the age of forty-five, and is much commoner in men than in women. The commonest site is at the level of the bifurcation of the trachea, the upper and lower ends of the œsophagus being next in order of frequency. There is, however, a distinct difference in the sites of incidence in the two sexes. Kelly, for example, found that of his cases of cancer in the hypopharynx and upper end of the œsophagus 75 per cent. occurred in women, whereas of œsophageal cancer elsewhere over 80 per cent. occurred in men. It is interesting to note that recent observations in Sweden and Holland show that in a high proportion of œsophageal cancer in women the disease has followed microcytic anæmia with dysphagia (p. 462). The growth presents considerable variations in its character, but we may say there are two chief types, viz. a hard contracting type, and a soft or encephaloid type. The former is usually comparatively localised, and by its growth round the tube and the resulting contraction a considerable degree of stenosis is produced. The softer varieties involve a greater extent of the œsophagus, form irregular projections into the lumen, and thus tend to cause obstruction (Fig. 326). At the same time, the destruction of the muscular tissue by infiltration interferes with the power of contracting. The growth not infrequently spreads upwards and downwards in the submucous tissue and forms secondary growths which raise up the mucosa; in this way an appearance as of multiple foci of growth may be produced. In the majority of cases the tumour is of the type of squamous epithelioma, occasionally it is a small-cell carcinoma with solid alveolar arrangement; the occurrence of adeno-carcinoma also has been described. In addition to causing obstruction, the tumour may produce important results by extension to adjacent parts. It may spread to the trachea or a bronchus, and ulcerate through the wall. Decomposing fluids then are likely to pass down the bronchi and give rise to septic or gangrenous pneumonia. In other cases, though less frequently, ulceration into the aorta may result and fatal hæmorrhage may be produced. Secondary growths occur in the lymphatic glands, and occasionally also in the internal organs, e.g. the liver; but death is usually caused by the local lesions. *Sarcoma* of the œsophagus is relatively rare. In character it resembles the softer varieties of cancer, but its growth may be more massive. In a few instances rhabdomyoma (p. 215) has presented malignant characters.

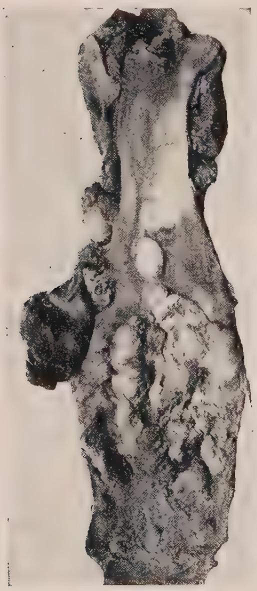

FIG. 326.—Extensive ulcerating Carcinoma in middle part of Œsophagus.

Congenital Abnormalities. In addition to stenosis or dilatation already mentioned, there may be various degrees of atresia of the œsophagus. The commonest of these is a condition in which the upper part forms a blind sac which is separated from the lower part, while the latter is patent and communicates with the trachea a short distance above its bifurcation. Sometimes, though in a minor degree, a similar abnormality is met with when the œsophagus is patent throughout; there is a communication with the trachea at the site mentioned and this may be of quite small size. In such a condition material from the œsophagus may pass into the trachea and set up a suppurative or gangrenous pneumonia. And, as has been mentioned, merely a small pouch or depression may be present in the œsophagus, representing the site of such an opening which has become closed.

THE STOMACH

If we compare the diseases of the stomach with those of the intestines, we find that the most important difference is that, whilst in the latter, specific bacterial infections—typhoid, dysentery, etc.—are comparatively common, such conditions are rarely met with in the stomach. This is in great part due to the bactericidal action of the gastric juice, which rapidly destroys most spore-free bacteria entering with the food, and when digestion has been completed and the contents of the stomach have been passed on to the intestine, the normal stomach soon reaches a stage of practical sterility. Organisms in the food may, however, escape this action of the gastric juice, especially when its condition is not quite normal, so that they reach the bowel in a living condition and may there lead to infection. This may not be the whole explanation of the peculiarity referred to, but it is no doubt an important factor. In addition there may be a greater resistance of the mucosa of the stomach than of that of the bowel. In any case, disease of the stomach is rarely of bacterial origin in the first instance. Improper diet, including drink as well as food, and various states of general malnutrition, fevers, anæmia, etc., are usually the conditions which lead in the first instance to gastric disorder. If, however, the stay of the food in the stomach is prolonged, and this is accompanied by imperfect digestion as is often the case in a dilated stomach, there may occur an abundant overgrowth of organisms of various kinds, as will be described below.

CIRCULATORY DISTURBANCES

Acute congestion is, of course, caused by irritants of the various conditions which lead to acute catarrh, but its presence is often obscured by post-mortem change. *Chronic congestion* occurs in cardiac and pulmonary disease and especially in obstruction to the portal circulation in cirrhosis of the liver. The mucous membrane becomes swollen and has a somewhat purple or livid appearance, whilst towards the pylorus there may be a slate-grey coloration, or minute brown points resulting from capillary hæmorrhages may be present. The changes of chronic catarrh are often superadded. In long-continued portal obstruction there may be marked varicosity of the veins around the cardiac orifice as well as at the lower end of the œsophagus, and serious hæmorrhage may occur from them. Fig. 328 shows a large varix produced in this way, which caused fatal hæmorrhage.

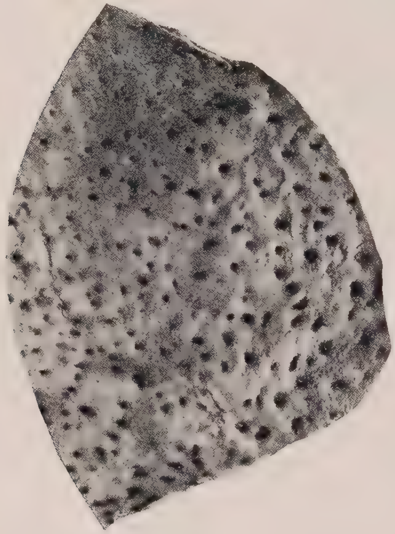

FIG. 327.—Multiple minute Hæmorrhages and Erosions in Stomach. × $\frac{3}{4}$.

Hæmorrhages into the mucosa occur in a variety of conditions —in chronic congestion, in purpura, in severe anæmia, and in infective fevers, etc. Sometimes there are numerous hæmorrhagic points of the size of pin-heads scattered over the mucosa, especially in the fundus, and they often are more marked along the summits of the folds. They are usually of a dark brown colour and the mucous membrane over some of them has been eroded so that minute ulcers are formed. The term *hæmorrhagic erosion* is applied to lesions of this type (Fig. 327). Some of the erosions may be free from pigment owing to its being removed by ulceration; occasionally, though rarely, they become confluent and of larger size. Hæmorrhagic erosions are met with in a variety of conditions, but chiefly in chronic hyperæmia and in septic diseases. They are commoner in children than in adults; not infrequently they are preceded by vomiting, and it would appear as if they were then the result of mechanical interference with the circulation, caused by the muscular contraction. In septic conditions small hæmorrhages are sometimes due to plugging of small vessels with cocci; we have seen them, for example, in pneumococcus septicæmia, but in most cases they appear to be the result of toxic action.

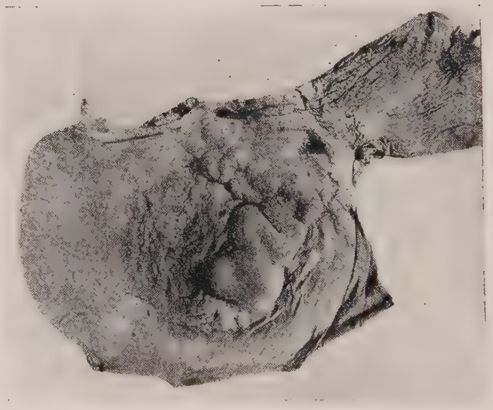

FIG. 328.—Large injected Varix at Cardiac Orifice of Stomach from a case of Cirrhosis of the Liver.

Fatal hæmorrhage occurred from the perforation seen at lower end of œsophagus.

Actual *bleeding into the cavity* of the stomach occurs in a number of gross lesions, such as peptic ulcer, carcinoma, varicose veins at cardia, etc. (Fig. 328). It occurs in splenic anæmia and in hæmorrhagic diseases of the new-born. There may be, however, a considerable amount of diffuse hæmorrhage from the mucous membrane without any discoverable breach of continuity; this is seen, for example, in severe septic conditions, in yellow fever where it gives rise to 'black vomit,' in cases of toxic jaundice, and occasionally without discoverable cause. The blood effused into the stomach becomes mixed with its contents and acquires a brownish or almost black colour, or there may be fragments of brownish coagulum mixed with the fluid. In cases of rapidly fatal hæmorrhages, however, the stomach may be filled by a large coagulum which forms a sort of cast of the interior, and the colour of the blood may be little altered. Such a condition may result also when the blood has passed down from the œsophagus, for example, from the bursting of an aneurysm into the lumen. Severe hæmorrhage arising in the stomach is usually the result of gastric ulcer or of ulceration of varicose veins; it is comparatively uncommon in carcinoma. When there has been a considerable hæmorrhage into the stomach, there is generally to be found, *post mortem*, altered blood in the small intestine and not infrequently in the large intestine also.

INFLAMMATORY CONDITIONS

(A) **Acute Gastritis.** The swallowing of irritants, hot fluids, alcohol in excess, unsuitable food with subsequent fermentative change, etc., may set up an acute gastric catarrh. This may also occur in acute fevers, notably in abdominal influenza, and in acute food poisoning. No doubt the ordinary changes seen in a mucous membrane are present, though it is difficult to find them in clear form owing to post-mortem changes. Superficial necrosis of the mucosa with fibrinous exudation, constituting a *membranous* or *croupous gastritis*, may occur also, but apart from the action of chemical irritants, it is rare; it is sometimes met with in septicæmic conditions and fevers, e.g. typhoid; and true diphtheria of the stomach also has been described. Another form called *phlegmonous gastritis* is very uncommon, but it possesses characteristic features. It is described as appearing in two forms, a diffuse and a localised, and it is produced by the entrance of organisms, usually streptococci, through an ulcer or some small lesion in the mucosa, the organisms afterwards extending widely in the submucosa and causing intense inflammation with fibrinous or semi-purulent exudate. The affected parts, which may be of great extent, have a thickened and stiffened character, and, on section, the mucous membrane is seen to be raised up by the yellow phlegmonous infiltration underneath. Phlegmonous gastritis is believed to occur especially in alcoholics.

(B) **Chronic Catarrh.** This is a relatively common condition, and in most cases it is associated with thickening of the mucous membrane, especially in the pyloric segment; it is sometimes known by the somewhat unsuitable name of *hypertrophic catarrh.* It may result from chronic alcoholism, the fermentations of chronic dyspepsia, the swallowing of septic material from the mouth, etc. Its occurrence is favoured by chronic venous congestion—as in portal obstruction or in cardiac disease. The mucous membrane affected becomes thickened and rather firmer, and its surface is somewhat granular showing slight elevations or even nodosities—the so-called *état mamelonné* of French writers (Fig. 329). It often presents a slate-grey colour, due to pigment derived from small hæmorrhages into its substance. Such a condition may be present also in the first part of the duodenum. Minute mucous cysts may be present in the affected mucosa from obstruction of the orifices of the glands, and occasionally small polypoid growths may be present. In rare instances the latter may be numerous and increase in size, so that the lining of the stomach becomes studded with polypoid masses (Fig. 338). In cases of chronic catarrh, ulcers or superficial erosions may sometimes be formed—*catarrhal ulcers*; they may arise from dilated glands, lymphoid follicles or possibly from small hæmorrhages.

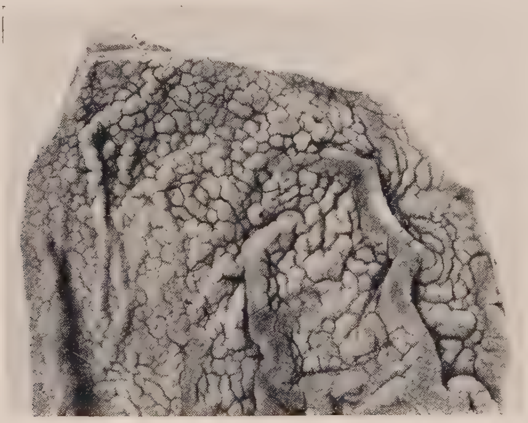

Fig. 329.—Portion of Stomach Wall in chronic Catarrh, showing irregular and nodular thickening (état mamelonné).

On Microscopic Examination of the stomach wall in chronic catarrh there is seen to be considerable desquamation of the surface epithelium and of the lining of the upper parts of the glands. There is also new formation of connective tissue and blood vessels with leucocytic infiltration, these changes being most marked in the superficial part of the mucosa; in fact, in this region much of the epithelium may have disappeared (Figs. 330, 331). The configuration of the glands becomes irregular, some being atrophied, others enlarged and, it may be, dilated to form small cysts ; many of the secreting cells become changed to mucin-forming cells. The chronic inflammation may extend to the deeper coats. It is hardly necessary to point out that when such structural changes have occurred a return to normal is no longer possible.

Another variety is *atrophic catarrh*. It is sometimes said to be the sequel of the so-called hypertrophic form, but we do not think this is usually the case. There is clear evidence that a constitutional element is concerned. The mucous membrane becomes much thinned and abnormally smooth, and there is marked atrophy of the glands. It may be associated with dilatation of the stomach, but whether as cause or effect, is often doubtful. The condition is of obscure nature and may sometimes be of neuropathic origin. It may lead to achlorhydria.

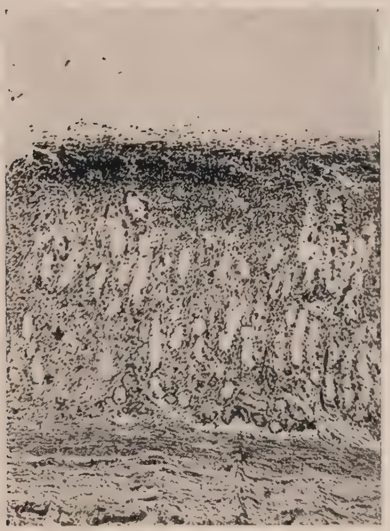

FIG. 330.—Chronic Gastric Catarrh, showing loss of Epithelium of upper parts of Glands with formation of young Connective Tissue ; lower parts of glands are becoming somewhat irregular. × 40.

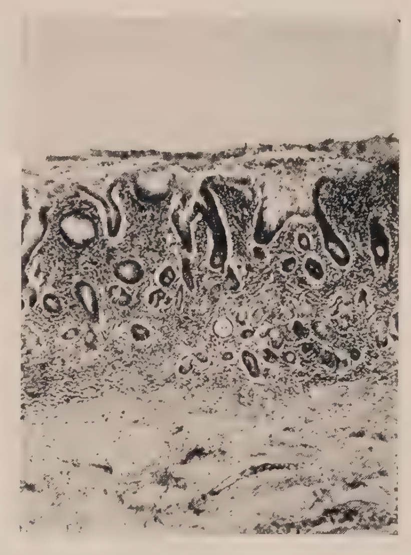

FIG. 331.—Atrophic Gastric Catarrh, showing marked thinning of Mucosa and irregularity of the Glands. × 40.

These atrophic changes are of great importance in view of their effects on the gastric secretion. The effects vary in degree and kind, thus :—(*a*) varying degrees of hypochlorhydria up to achlorhydria, (*b*) the rarer condition of complete achylia—absence of digestive ferments along with achlorhydria, and (*c*) absence of the intrinsic factor necessary for normal hæmopoiesis resulting in pernicious anæmia, this being associated with either (*a*) or (*b*).

The term *cirrhosis of the stomach* has been applied to a rare condition in which there is a more or less general fibrosis with stiffening of the stomach wall, resulting in what has been called "leather-bottle stomach." The term *linitis plastica* also has been applied. Such a condition is, however, usually due to diffusely spreading carcinoma (p 543) ; in fact it has always been so in my experience. The possibility that it may also be produced by an inflammatory condition must, however, be admitted. It might conceivably result from a healed phlegmonous gastritis, if such occurs. Localised fibrosis of course occurs in connection with a chronic ulcer, and may sometimes spread widely.

Action of Corrosive Poisons. Only the main facts with regard to these can be given. If we consider first the effects of the more powerful corrosives which produce much necrosis of tissue, we may say that there are three types of change :—

(A) *Mineral acids* cause extensive destruction of the stomach wall attended by much hæmorrhage and sometimes by actual perforation. Sulphuric acid is specially destructive ; some of the parts may be almost black or charred in appearance, whilst in others less affected, extravasated blood, variously altered, may be present. Perforation is not uncommon and the effects of diffusion of the acid into neighbouring parts are often evident. The action of hydrochloric acid is less intense ; hæmorrhage may be marked and widespread, or necrotic areas of paler colour may be present. Nitric acid usually causes a brownish-yellow or greenish colour owing to the formation of xanthoprotein.

(B) The second type of action is extensive necrosis with softening of the tissues, and is seen in the case of the *caustic alkalies*. Portions of the stomach wall may be changed into soft necrotic material of somewhat gelatinous appearance ; here also perforation may occur.

(C) The third type of action is *coagulation* of the tissue proteins, by which the lining of the stomach becomes fixed, and the cellular structure may actually be preserved. This is well seen in carbolic acid poisoning, where the mucosa has a stiff corrugated appearance and a greyish colour. It is produced also by corrosive sublimate, and we found it to be a well-marked feature in a case of poisoning with a strong solution of zinc chloride.

A large number of poisons of less intense action produce chiefly inflammatory changes attended with a varying amount of hæmorrhage, superficial necrosis, or membranous exudate. To this group belong weaker acids, such as oxalic acid or acetic acid, various metallic salts, arsenic, antimony, etc. Arsenic (arsenious acid) causes an intense inflammation with white patches of tenacious mucus or exudate in which collections of the poison are present. Antimony causes a general acute inflammation, whilst in phosphorus poisoning there are usually hæmorrhages and fatty degeneration in the mucosa. For details, however, special works on toxicology must be consulted.

Specific Infections. These are comparatively rare in the stomach as compared with the bowel, and this is due largely to the fact that most spore-free organisms are killed by the action of the gastric juice. Small *typhoid* ulcers arising in connections with the lymphoid tissue have occasionally been met with, but they are very rare. Primary *anthrax* lesions produced by the swallowing of the spores, have occasionally been observed; they present characters similar to those in the small intestine (p. 563). *Tuberculous* ulcers are met with, but they are relatively uncommon; they are seen especially in children with pulmonary cavities. The ulcers are usually superficial and of small size, and their mode of formation and general characters correspond with those of tuberculous ulcers of the intestines. They are apparently the result of swallowing bacilli, but some writers suppose that they may be of hæmatogenous origin. *Syphilitic* lesions, though rare, occur both in the congenital and acquired forms of the disease. In the latter, the lesion starts in the submucosa in the form of a diffuse infiltration or gummatous mass, and secondary ulceration may follow. The lesion may sometimes reach a considerable size and may simulate carcinoma; sometimes hæmatemesis may be produced and achlorhydria may be present. Spirochætes have been found in such lesions, e.g. by McNee, so that there is no doubt as to their nature. The histological changes correspond with those met with in syphilitic lesions elsewhere.

Gastric Ulcer.[1] The occurrence of hæmorrhagic erosions and catarrhal ulcers has already been described, but the all-important form of ulceration of the stomach is that in which the action of the gastric juice is concerned. It is thus called *peptic ulcer*, though frequently spoken of simply as gastric ulcer, sometimes as *perforating ulcer*. This form of ulceration is met with not only in the stomach but in other parts exposed to the action of the gastric juice, that is in the first part of the duodenum or duodenal bulb, and occasionally at the lower end of the œsophagus. Further, in cases where gastrojejunostomy has been performed, ulceration occasionally occurs in the part of the jejunal wall exposed to the action of the gastric juice, especially when the acidity of the latter is increased. Gastric ulcer is often stated to be commoner in women than in men. Recent statistics, however, show that it is commoner in the male sex than was formerly supposed, and according to some writers the incidence in the two sexes is approximately the same. It is possible that variations in this respect may occur in different localities according to the conditions of life. Our own experience is that gastric ulcer is now less frequent in women than was formerly the case, and this is probably due to the rarity of chlorisis, a condition with which it was often associated. There is no doubt, however, that duodenal ulcer is distinctly more frequent in the male than in the female sex, the proportion being about 3 : 1. In the male duodenal ulcer is distinctly commoner than the gastric form.

VARIETIES. Any distinction of types of ulcer must be artificial as intermediate varieties occur, but we may follow Stewart's classification and recognise three main classes—(*a*) acute, (*b*) subacute, and

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[1] For full details see *Gastric and Duodenal Ulcer*, by Arthur F. Hurst and Matthew J. Stewart, London, 1929.

(c) chronic. *Acute* ulcers involve only the mucosa and submucosa; they are usually small, but occasionally may reach a considerable size. They may be single, multiple or in large numbers. Unlike the chronic forms, they have a wide distribution and the general result is healing without visible scar. The *subacute* ulcers are fewer in number and not infrequently single. They extend down to the muscular coat and may even partly invade it, and, like the chronic type, are commonest in the lesser curvature. The *chronic* gastric ulcer is solitary in the vast majority of cases; Stewart found two chronic ulcers in less than 3 per cent. of his cases and never more than two. It is generally agreed that the commonest site of chronic ulcer is the lesser curvature from two to four inches from the pylorus; next in frequency comes the pyloric canal, while other sites are rare. Stewart estimates the minimum age of a 'chronic' ulcer to be two months and regards complete breach of the muscular coat as one of its most important features. The acute peptic ulcers rarely produce any definite symptom except hæmorrhage, which occasionally may be severe. But an ulcer of this type may occasionally lead to comparatively rapid perforation. Such an ulcer, which may suitably be called 'acute perforating,' was according to our experience much more common forty years ago than it is now, and appeared to be especially related to chlorosis. It would also appear to us that duodenal ulceration is commoner than it used to be and especially that comparatively large chronic duodenal ulcers are more frequent. It seems that there has been a distinct change with regard to the incidence of different types of peptic ulcer. We may now give an account of the characters of gastric ulcers, selecting the acute perforating ulcer and the chronic ulcer as types.

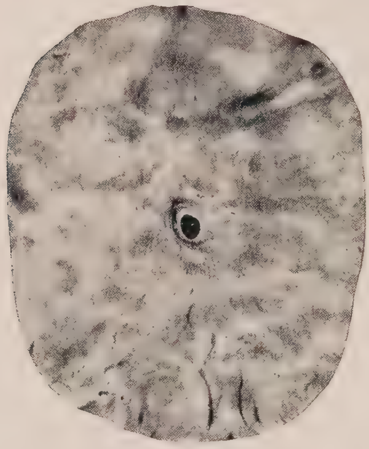

FIG. 332.—Acute Gastric Ulcer with Perforation.

STRUCTURAL CHANGES. An ulcer of the more *acute perforating* variety is usually round or slightly oval in shape and is not often larger than a sixpenny piece; usually it is smaller. Its margins are smooth and regular and it has a punched-out appearance (Fig. 332). Such an ulcer may have penetrated the whole thickness of the wall; in which case, when viewed from the inside it has often a terraced appearance owing to the fact that the apertures in the different coats diminish from within outwards. This is the type of acute ulcer which gives rise to perforation, and this may occur quite suddenly.

As we have said, it is now less frequently met with than formerly. It may be solitary, but is sometimes associated with other ulcers in an earlier stage of formation. Ulcers of the *chronic* type reach a much greater size; the largest are usually somewhat oval in form and may measure two inches or even more in the long axis (Fig. 333). The ulcer may still be bounded by the outer part of the stomach wall, and in this case its floor is usually smooth and fibrous while the tissue around is somewhat indurated. More frequently, however, fibrous adhesions are present over the ulcer and its base is firmly fixed; and when the ulcer has become large it may have extended right through the wall into some adjacent part, usually the pancreas or liver. It may occasionally burrow through the diaphragm or even into the bowel. When this extreme stage has been reached the margin is fairly smooth and overhangs somewhat, the ulcer is deep, and its floor is firm and often irregular or nodular, being constituted by a fibrosed layer of the viscus which has been involved. Perforation in this chronic type is often prevented by fibrous thickening and adhesions, but occurs in about a third of cases, usually at one margin of the ulcer. It is due to a more rapid necrotic process and is commonest in the comparatively rare ulcers in the anterior wall owing to its mobility. Occasionally the actual rupture may be produced mechanically, for example, by stretching the body. Erosion of a large artery in the floor of a chronic ulcer is a not uncommon occurrence and may lead to fatal hæmorrhage. The microscopic appearances in chronic ulcer are illustrated in Figs. 334 and 335.

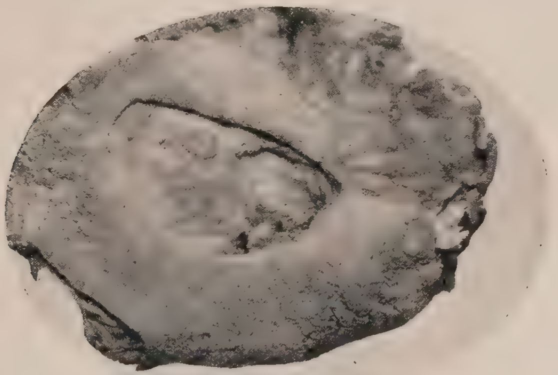

FIG. 333.—Large chronic Gastric Ulcer from posterior Wall near lesser Curvature.

The nodular floor is constituted by indurated pancreatic tissue. × $\frac{3}{4}$.

Ulcers in the *duodenum* have the same general characters as those in the stomach, but do not reach so great a size. One type is a small ulcer of about a quarter of an inch in diameter, which may penetrate the whole wall, the appearance being as if a small hole had been punched out. Duodenal ulcers are, however, as a rule much larger (Fig. 336), and those on the posterior wall are larger than those on the anterior. Usually there is a single ulcer either on the anterior or on the posterior wall, but Stewart found two ulcers present in about 17 per cent. of the cases. Not infrequently, two ulcers oppose one another at a corresponding level, the so-called 'kissing ulcers.' Perforation is almost confined to ulcers on the anterior wall. On the other hand, severe hæmorrhage usually occurs from posterior wall ulcers. A frequent position of ulceration is the upper part of the duodenum just beyond the pyloric sphincter. The acute type of duodenal ulcer has been found occasionally in young infants.

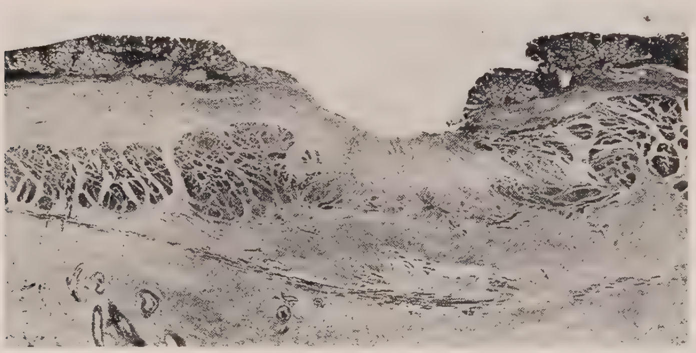

FIG. 334.—Early chronic Gastric Ulcer, showing Fibrotic Replacement of Muscular Coat. (J. S. F. N.) × 7.

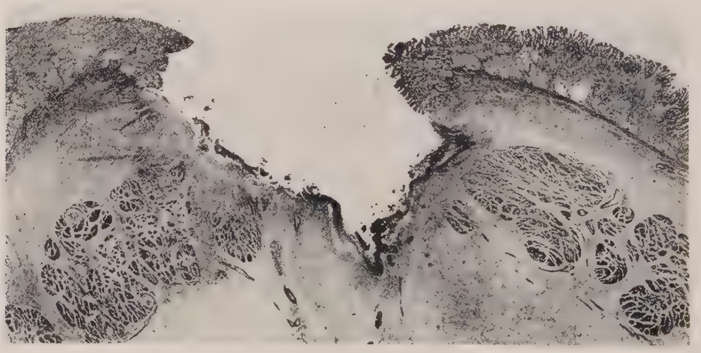

FIG. 335.—Chronic Gastric Ulcer at later stage, showing Breach of Muscular Coat. (J. F. H.) × 7.

When a gastric ulcer is examined microscopically in the more acute stage, a remarkable feature is the comparative lack of inflammatory reaction in connection with it. There may be some necrotic material on the floor and at the margins, also some leucocytic infiltration, but the ulcer on the whole has a clean-cut appearance. In the chronic stage, however, there is much fibrosis around and beneath, and not infrequently obliterative changes can be seen in the arteries. The muscular coat at the site is interrupted and replaced by fibrous tissue.

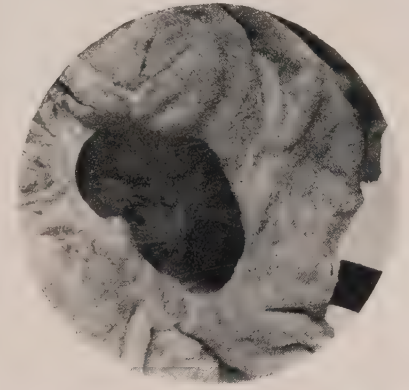

Fig. 336.—Large chronic Ulcer of Duodenum just beyond the Pylorus.

The ulcer had perforated at the margin, as is shown by the piece of whalebone. × $\frac{4}{5}$.

Results. (1) *Healing and Cicatrisation.* The acute peptic ulcers usually undergo healing and leave no visible cicatrix. Healing is the rule also in the subacute type and it is common too in the chronic type, even if the ulcer is of considerable size, as is shown by the presence of scars and contractions.

If the ulcer has been comparatively superficial, the scar may be scarcely noticeable or there may be merely a small depression with smooth whitish surface; if, on the other hand, it has penetrated somewhat deeply, there is often a radiating indrawing of the mucous membrane around, so that a sort of stellate appearance results (Fig. 337). The healing of an ulcer at the pylorus often leads to *stenosis* of the opening owing to the cicatricial contraction, and considerable dilatation of the stomach may follow. In such a condition the muscle of the pylorus is apt to be thickened and œdematous, and the appearance may suggest the existence of a scirrhous carcinoma; only microscopic examination can determine the true nature of such a condition. It may be noted, however, that in Stewart's series of cases, stenosis of the pylorus was more frequently of duodenal than of gastric origin, being caused by a chronic ulcer of the duodenum close to the pylorus. This is more likely to happen with ulcers on the posterior wall as they tend to be larger. Duodenal stenosis may occasionally occur in a similar way at a lower level. The healing of an ulcer in the lesser curvature may be attended by much fibrous overgrowth both on the anterior and posterior walls, and contraction of the tissue may produce a narrowing of the stomach about its

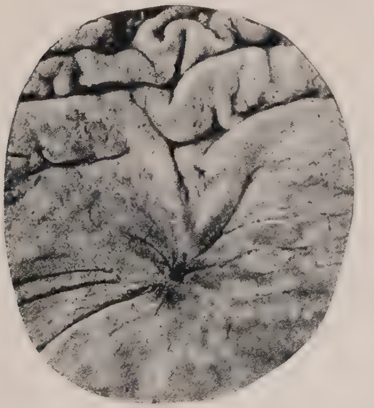

Fig. 337.—Healed Gastric Ulcer with stellate Cicatrix.

middle so that an '*hour-glass*' condition results. In some cases the chief result is a shortening of the lesser curvature. Stewart found that 'hour-glass' contraction was rather more frequent than pyloric stenosis of gastric origin.

(2) *Septic Infections.* In the second place, various inflammatory and suppurative conditions may be produced by bacterial infection from the ulcer. In some cases, as has been mentioned, rapid perforation may take place and the stomach contents escape into the general peritoneal cavity or, posteriorly, into the lesser sac. The pain, abdominal rigidity, and symptoms of collapse which follow are caused by the acid gastric contents; these, in many cases, are practically sterile at first, but organisms soon gain a foothold and acute peritonitis results. In other cases infection of the peritoneum may occur before there is actual perforation, and thus the surface may be glued to adjacent parts by fibrinous exudate. This is more likely to happen posteriorly and in the region of the lesser curvature, where the movements of the stomach are less than in other parts. The inflammatory condition may remain localised and fibrous adhesions take place, or, on the other hand, a localised suppuration may result; thus a localised collection of pus may form in various situations, and not infrequently suppuration extends over the surface of the liver, giving rise to a subphrenic abscess, which may infect the pleura. Occasionally, though rarely, bacterial invasion of a vein may occur and secondary abscesses be produced in the liver (p. 609).

(3) *Hæmorrhage.* This is of common occurrence and varies greatly in degree. Often there is oozing of blood either from an acute or a chronic ulcer. The blood may be in considerable quantity and give rise to coffee-ground vomit, or to blood in the stools, which may have a tarry character. On the other hand, the blood may be in small quantity and may be detectable in the stools only by chemical examination. Sometimes, however, an artery of considerable size may be eroded and a large hæmorrhage take place, leading to fatal results. This occurs chiefly in the case of a large chronic ulcer which has come to involve an artery outside. The artery becomes incorporated in the floor, and in most cases becomes obliterated by endarteritis, but sometimes this does not happen, and the wall of the vessel becomes weakened by the digestive process and rupture follows. Occasionally a small aneurysm forms first. In a case of fatal hæmorrhage one can usually find the eroded artery in the floor of the ulcer. Severe hæmorrhage from duodenal ulcer is commonest when the ulcer is in the posterior wall.

(4) *Development of Carcinoma.* Sometimes carcinoma arises in connection with a chronic gastric ulcer, but there is great diversity of opinion as to the frequency with which this occurs. Stewart found that evidence of previous chronic ulcer was present in about 15 per cent. of cases of carcinoma and most recent figures agree with this. In judging of the relationship there must be clear evidence

of cancer in connection with an ulcer, as there is often irregular growth of epithelium and even displacement of epithelium or heterotopia at the margin of an ulcer apart from any malignancy. As to the pre-existence of chronic ulcer in an undoubted case of carcinoma, a very important point as insisted on by Stewart, is that in chronic ulcer the muscular coat has become entirely destroyed and replaced by a more or less fibrotic tissue in which there is often obliteration of arteries. On the other hand, whilst carcinoma often invades the muscularis it practically never destroys it entirely, and even in advanced cases remains of muscle are to be found between the cancer cells.

Causation. Whilst the special characters of gastric ulcer are due to the action of the gastric juice, the exact causation is imperfectly understood. Even the existence of a local lesion is not sufficient to explain the process, because it is well known that wounds and other lesions of the stomach rapidly undergo healing in the normal state. There are thus two problems, viz. (1) the origin of the local lesion and (2) the cause of its progressive character. With regard to the first, the general characters of some peptic ulcers suggest the possibilities of a vascular lesion. It has been shown experimentally, that ulcers may be produced by embolism of the arterial branches in the stomach, but this occurs only occasionally and seems to require multiple blocking for its production. However, in most cases of gastric ulcers there is no source of embolus to be found, and it may be said that embolism can play a part only in quite exceptional cases, if at all. There is no more evidence that thrombosis is concerned. If a vascular lesion is concerned, there remains then only the possibility that it may result from spasmodic contraction of a small artery or a portion of the muscular coat. With regard to such explanation it is not possible to say anything definite, but the occurrence of hæmorrhagic erosions, apparently due to vomiting, makes it quite conceivable that vascular spasm, possibly associated with irregular contraction of the stomach, may play a part.

As stated above, multiple acute ulcers are not infrequently met with in infective and septic conditions. Most of these heal but a few become subacute, and it would appear that of the latter only a few fail to heal and become chronic ulcers. One cannot, however, regard a single ulcer as always representing the sole survival of such a process and it is difficult to explain why a chronic ulcer is so often solitary.

Cushing recently brought forward evidence which indicates that a nervous element may be concerned. He found that there is a centre in the diencephalon, apparently tuberal in position, from which certain parasympathetic tracts pass, and that experimental lesions in the course of these are prone to cause gastric erosions, perforations or ulcers. Thus there is the possibility that the centre or the fibre may be affected in various ways and that interference with digestion, hyperacidity, etc., may result.

The second question is as to the persistence and enlargement of peptic ulcers. It is now well established that in the majority of cases there is either an increased concentration of hydrochloric acid in the gastric juice—hyperchlorhydria—or a high normal value. In duodenal ulcer hyperchlorhydria is still more frequent and more marked. Hurst considers that what he has called 'the hypersthenic gastric diathesis' is the essential predisposing cause of duodenal ulcer. This inborn variation from the average normal is characterised by a short stomach with active peristalsis and rapid evacuation, and by hyperchlorhydria with digestive hypersecretion. An important condition favouring extension, once a local lesion has been established, is thus usually present in peptic ulceration. Conditions of anæmia and general malnutrition will no doubt act by lowering the resistance of the tissues. The importance of the acid gastric juice has also been emphasised by experiment. If the pylorus is closed and the duodenum removed and the jejunum is then anastomosed to the stomach while the bile and pancreatic ducts are transplanted into the jejunum, ulcers may form in the latter and a certain proportion of these are of the solitary chronic type (Mann and Bollman). It has also been shown by another procedure that bile and the secretions of the pancreas and duodenal mucosa have a certain protective action against the gastric juice. All the facts available go to show that hyperchlorhydria is the most important factor in leading to the characteristic features of gastric and duodenal ulcers.

Dilatation of the Stomach. This may be conveniently described as of two main types, namely (1) dilatation due to obstruction at the pylorus and (2) dilatation occurring without obstruction. The former results from the scar of a gastric or duodenal ulcer or from a scirrhous cancer at the pylorus, occasionally from fibrous adhesions outside the stomach at the pyloric region. It may be due also to a degree of congenital stenosis of the pylorus, insufficient to cause death. In these conditions, along with the dilatation there is a varying amount of muscular hypertrophy which is most marked in the pyloric segment; and it must be borne in mind that the increase in muscle appears less than it actually is, owing to the dilatation. In the production of dilatation without obstruction, a number of factors are concerned—catarrhal changes, atony of the muscle, and fermentative changes; and any one of these may lead to the others. Deficiency in gastric juice may lead to longer retention of the food in the stomach and fermentative changes are more apt to occur. Atony of the muscle will lead to the same result, and in many cases a sort of vicious circle is set up. Atonic dilatation occurs after acute fevers and may pass into a chronic condition, and it is not infrequently found in association with neurasthenia and hysterical conditions, though it is often difficult in such cases to say which is the primary event. The stomach may reach a large size and may sometimes be displaced downwards as a whole in the abdominal cavity—*gastroptosis.* The duodenum is not infrequently dilated at the same time, but there may be a kink in it and this may intensify the dilatation. Acute dilatation of the stomach is occasionally met with after abdominal operations, quite apart from septic infection, and seems to be a paralytic condition resulting from handling. The distension can often be relieved by the passage of a tube. In the contents of a chronically dilated stomach there is often an abundant growth of various organisms, especially yeasts, sarcinæ, hyphomycetes, etc., and these lead to fermentative changes, often attended by the formation of lactic and butyric acids and by a considerable evolution of gas. There is, as a rule, little growth of cocci and bacilli unless there is a marked reduction or absence of hydrochloric acid, such as is common in cases of carcinoma (p. 546).

TUMOURS

Of simple tumours the form most frequently met with is the *papilloma* or pedunculated adenoma, which varies somewhat in character. Sometimes there is a large proportion of connective tissue as a core, sometimes the mass is composed mainly of glandular elements with thin bands of stroma between ; then again, the surface may be comparatively smooth or covered by papilliform processes. Papilloma is met with most frequently in the pyloric region where there may be multiple growths, but in some cases almost the whole of the stomach may be beset with polypoid excrescences, and this condition is accompanied and apparently preceded by a chronic catarrh (p. 530). Along with marked evidence of this condition, there may be very numerous minute papilliform projections, and in addition larger polypoid growths (Fig. 338). Occasionally, carcinoma may develop in connection with

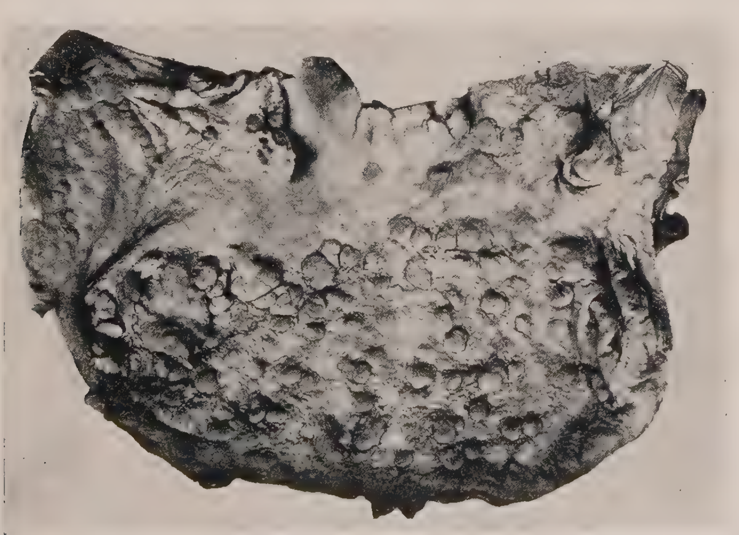

Fig. 338.—Multiple Papillomata of Stomach, showing numerous Nodules in various stages of formation.
The patient was a chronic alcoholic.

a simple papilloma. *Leiomyoma, fibroma*, and *lipoma* occur also, but are rare tumours. In cases of general neuro-fibromatosis, multiple fibromata are met with, chiefly on the surface of the stomach along the course of the nerves. Leiomyomata are usually small but sometimes reach a considerable size, and cases have been recorded where sarcomatous growth has become superadded and produced metastases. *Lymphangioma* also has been described.

Carcinoma. Of the malignant growths, carcinoma is by far the commonest. Its general characters vary greatly and it produces many different effects. The pyloric segment is the commonest site, next comes the lesser curvature; but cancer may occur in any part. It will thus be noted that the distribution of cancer differs from that of chronic ulcer. Stewart found that in carcinoma the pyloric canal was the primary site in 84·5 per cent. of cases, whilst in chronic ulcer the lesser curvature was the site in 94·3 per cent. So far as the naked-eye appearances are concerned, we may distinguish a scirrhous or hard variety and an encephaloid or soft variety, while mucoid or colloid cancer presents certain features of its own. In most cases the growth of cancer is mainly of the infiltrative type, but some soft cancers form large projecting masses, and sometimes in adeno-carcinoma shows papilliform upgrowths. As regards microscopic structure, a large proportion of the growths are adeno-carcinomata, whilst in others the epithelium is arranged in solid masses of cells in alveoli; but in the same tumour both types of growth may be present. This statement applies both to the hard and soft varieties.

Spread by the lymphatics is well illustrated in carcinoma of the stomach. From the primary focus in the mucosa, the growth spreads to the relatively wide network of lymphatics in the submucosa and thence throughout those of the muscular coat to the subseral network. In this way there is often a widespread injection of the lymphatic system. Extension takes place also upwards through the muscularis mucosæ into the mucosa and thus there sometimes results an appearance as if the growth were arising in multiple foci in the latter (Fig. 339). The possibility that there may sometimes be multiple foci of origin, however, cannot be entirely excluded.

The *scirrhous* type of cancer, commonest in the pyloric region, appears as an indurated area which gradually extends and undergoes ulceration. All the coats become involved, and the muscle in the neighbourhood, in addition to being infiltrated, is often hypertrophied and œdematous. There is a special tendency for the growth to spread around the pylorus and lead to stenosis, but it is noteworthy that there is rarely extension into the wall of the duodenum. Stenosis leads to dilatation of the stomach and its consequences (*vide* p. 540). In other cases the growth spreads diffusely through the gastric wall for a considerable area, giving rise to thickening and induration. This diffuse form of carcinoma, which is by no means rare, leads to a characteristic result. The stomach becomes small and its wall is stiff and increased in thickness—'leather-bottle stomach'

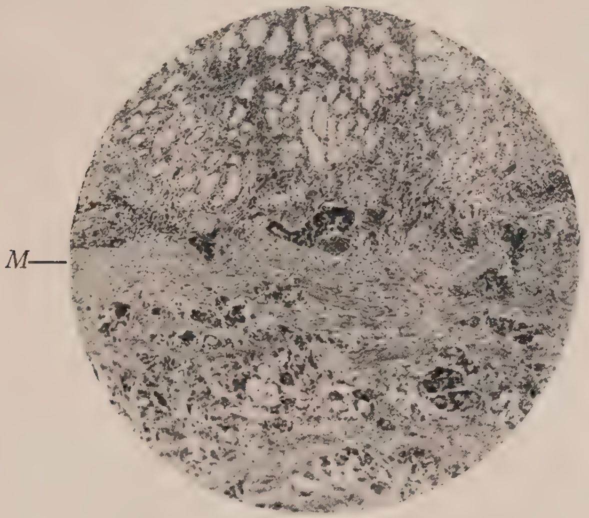

Fig. 339.—Section of Stomach Wall showing Infiltration of Lymphatics by Cancer Cells, seen as dark masses. + 60.

Note that, at places, the cells are growing upwards through the muscularis mucosæ (*M*) into the mucosa.

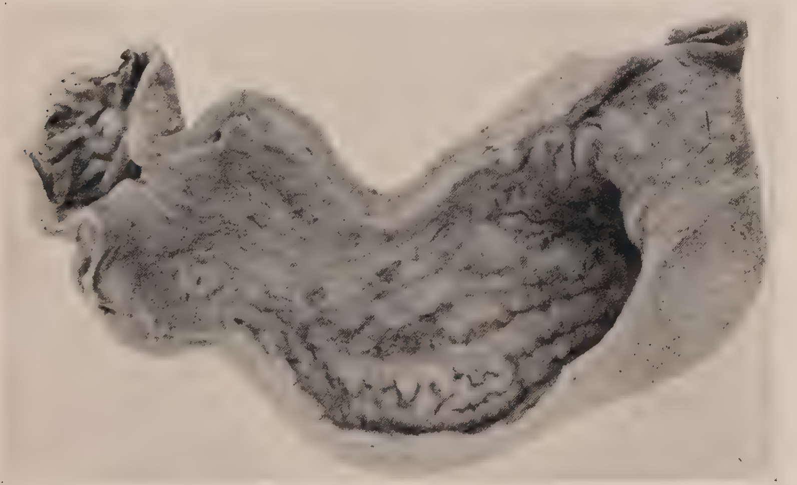

Fig. 340.—Diffuse Carcinoma of Stomach.

Note the general thickening of the wall without the presence of nodular growth and with little ulceration. × ⅔.

(Fig. 340). There may be no evidence of nodular growth and little or no ulceration, and the stomach has simply the appearance of being the seat of general fibrosis. Microscopic examination shows that the cancer cells are scattered throughout the tissue rather than arranged as clumps in alveoli. They are rounded and often contain droplets which give the reaction of mucin (Fig. 341). At places they are easily identified but they soon become atrophied and disappear in the stroma, so that only fibrous tissue remains. Occasionally it may be difficult to recognise the condition as malignant, but I have not yet seen a case of diffuse thickening of the stomach wall in which carcinoma was not found in some places. In saying this, however, I do not deny the possibility of a true inflammatory cirrhosis of the stomach. In the diffuse form of cancer the growth may occasionally spread to the wall of the bowel and the mesentery, leading there also to a general thickening and stiffening without the presence of recognisable nodules.

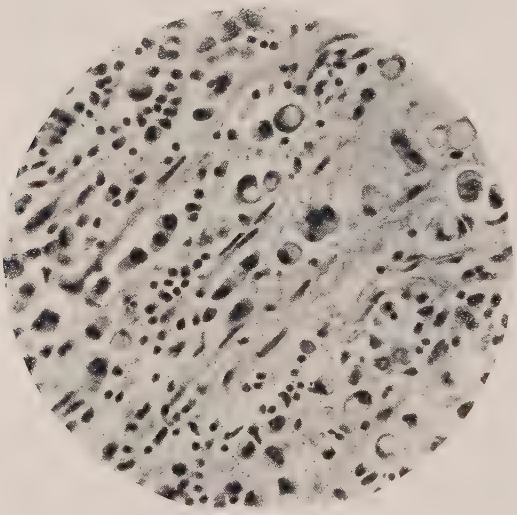

Fig. 341.—Diffuse type of Carcinoma in Muscular Coat of Stomach.

Note that the cells are irregularly scattered, some containing mucous globules and others showing atrophic change. × 300.

The softer or *encephaloid* types of cancer present a variety of characters, but, to speak generally, they are irregular masses of soft tissue which have a marked tendency to undergo ulceration and necrotic softening (Fig. 342). They occur not infrequently in the fundus and other parts, as well as in the pyloric region. Such a tumour may grow through the stomach wall and involve an adjacent organ by direct extension. We have seen, for example, a case in which direct extension of the growth took place to the transverse colon, and then, by necrosis and breaking down of its substance, a communication was formed between the stomach and the colon. Similarly, ulceration may occur into other parts.

Mucoid or '*colloid*' cancer, which, like the scirrhous, usually starts in the pyloric portion, is characterised by two features, viz. its diffuse mode of spread in the stomach wall and its tendency to invade the peritoneum. A large portion of the stomach may be the seat of infiltration, its wall becoming greatly thickened and stiffened and presenting a somewhat translucent appearance on section (Fig. 343). The wall of the stomach may be fully two inches thick at places and its lumen greatly reduced. When the peritoneum is invaded the growth may reach an enormous size, and the various

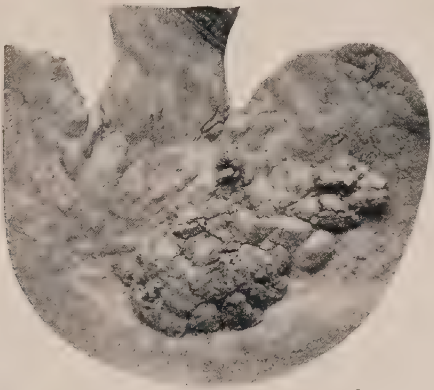

Fig. 342.—Encephaloid Cancer at Cardiac Orifice of Stomach, showing Necrosis and Sloughing. × ⅔.

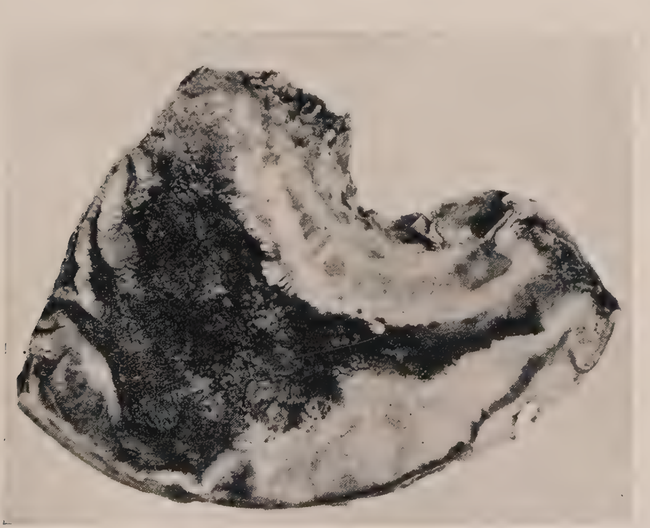

Fig. 343.—Mucoid Carcinoma at Pylorus, showing great Infiltration and Thickening of the Wall (viewed from behind). × ⅔.

structures are encased and glued together by masses of translucent tissue (Fig. 367).

In all types of cancer a widespread invasion of lymphatics in the stomach wall is apt to occur at an early period. This may be present in regions where no change is detectable by the naked eye. The lymphatic vessels and glands, especially in the lesser curvature, are early involved, and then extension to the glands in the portal fissure and to the substance of the liver soon follows. Widespread dissemination of growth in the liver, however, is usually due to spread by way of the blood stream. There is no doubt that secondary invasion of the liver occurs much more frequently and at an earlier period in gastric than in intestinal carcinoma. The cancer may spread through the wall of the stomach and involve the peritoneum, and when this occurs, there is often a widespread growth in the omentum, which becomes drawn up and greatly infiltrated. Numerous minute nodules may be scattered all over the peritoneal surface, and they are usually attended by a certain amount of inflammatory reaction and ascites. Extensive growth may occur in the pelvis, and in the female large masses may be present in the ovaries. The pleuræ and lungs are sometimes involved by lymphatic spread, and even the glands above the clavicle may be affected and be palpable during life. On the other hand, the infiltration may spread widely downwards, and we have seen the inguinal glands enlarged and the seat of secondary growth. These examples will serve to show how manifold and widespread the infiltration from gastric carcinoma may be.

Associated Conditions. Carcinoma is usually associated with alterations in the stomach contents. As a rule there is an abundant growth of micro-organisms of various kinds—torulæ, sarcinæ, cocci and bacilli. A large Gram-positive bacillus, known as the Boas-Oppler bacillus, is often to be found, but though its presence is very common, it cannot be taken as a pathognomonic of cancer as was supposed by some writers. The organismal growth results partly from stasis, partly from the necrotic tumour tissue becoming infected, and it is favoured also by the frequent absence of hydrochloric acid. It is to be noted that whilst a growth of various organisms may occur in any kind of dilatation, there is little growth of bacteria unless hydrochloric acid is absent or very deficient. Free hydrochloric acid is absent in the large majority of cases of gastric carcinoma, but not in all. There may be complete achlorhydria when the growth is very small and this is not the result of the growth but of the preceding chronic changes in the gastric mucosa. Most of the cases where free hydrochloric acid is present are those in which the carcinoma has developed secondarily to a chronic gastric ulcer, which is usually associated with hyperchlorhydria. Of course, achlorhydria is met with in other conditions, e.g. atrophic gastritis, pernicious anæmia, microcytic anæmia, as well as a constitutional peculiarity. It is considered by some that achlorhydria along with the presence of lactic acid is highly suggestive of carcinoma. There is, however, no one test by which carcinoma can be diagnosed. The secondary bacterial infection in the growth itself and in the stomach contents, is an important factor in leading to the cachexia and anæmia which accompany carcinoma. The secondary anæmia (p. 451) may be of severe degree. Anæmia of the megalocytic type has been observed to develop in connection with carcinoma, but is very rare. It will occur when the changes in the gastric mucosa have been such as to lead to absence of the ' intrinsic factor ' necessary for normal hæmopoiesis.

Of the *precancerous lesions* the most frequent are (*a*) chronic gastric ulcer, (*b*) papilloma or adenomatous polypus, and (*c*) chronic gastric catarrh. The occurrence of carcinoma in connection with the first has already been considered (p. 538). The origin of carcinoma from a simple papilloma, though less frequent, is still fairly common; Stewart found evidence of this event in 4 or 5 per cent. of cases of carcinoma. The importance of (*c*) chronic catarrh as a preceding condition, which is practically always present, has been insisted on by some writers, notably by Hurst. In addition it leads to the accompanying changes in the gastric secretion which have been referred to above.

Sarcoma is of rare occurrence, constituting about 1 per cent. of malignant growths of the stomach. It may be of various structural types, round-cell, spindle-cell, etc., and lymphosarcoma is met with. As a rule the growth is more localised than in the case of carcinoma, and tends rather to form a rounded projecting mass which may be of considerable size; naturally, ulceration and necrosis may follow. Multiple nodules, however, may be present, and lymphosarcoma may occasionally lead to a diffuse infiltration.

Congenital Abnormalities. The most important of these is stenosis of the pylorus. It is of not very rare occurrence at birth, and by the obstruction

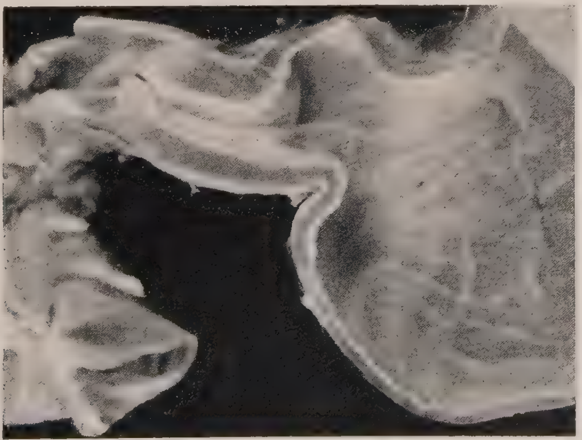

Fig. 344.—Congenital Stenosis of Pylorus. (J. W. S. B.)
The anterior wall at the pylorus has been cut away and the greatly hypertrophied muscle at the pyloric antrum is shown.

and persistent vomiting which it causes may lead to death. The condition is now often satisfactorily treated by operation. The obstruction is due to thickening of the wall at the pylorus, and this may extend back over a considerable distance, gradually fading off; or it may be more localised and in the form of a definite band (Fig. 344). The thickening is essentially due to hypertrophy of the muscle, the circular fibres especially being increased, whilst the lumen is narrowed to a varying, sometimes marked, degree. The nature of the condition is obscure. It is usually regarded as a hypertrophy produced by spasmodic contraction at the pylorus; but the nature of the exciting agent or neuro-muscular abnormality is not known. Another view is that it represents merely an abnormality in the process of growth.

Diverticula occur in connection with the stomach, either in the pyloric portion or in the region of the fundus, but they are rare. Occasionally the stomach is somewhat narrowed about the middle, a certain degree of so-called 'hour-glass' contraction being produced. Such a condition, however, occurs more frequently as the result of cicatrisation from an old gastric ulcer (p. 537).

THE INTESTINES

INFLAMMATORY CONDITIONS

The causes of inflammatory changes in the intestines may be conveniently arranged into three chief groups: (*a*) *Bacterial Infections*; (*b*) *Definite Poisons*, organic and inorganic; (*c*) *Disordered Digestion*, with fermentation and formation of irritating substances. The nature of the last is imperfectly understood, but organic acids are supposed to be of importance. It is now known that certain conditions which were formerly put under the name of 'food poisonings' are really of the nature of infections. In some cases of intestinal inflammation a recognised bacterium is the cause and may produce a characteristic lesion, whilst in other cases lesions often with ill-defined features occur and may be caused by a variety of bacteria. We may accordingly speak of *specific* and *non-specific* forms of inflammation.

Enteritis—*Non-specific.* The non-specific inflammations like those in the stomach may be of different types, the chief of which may be described as follows:

(A) *Catarrhal Enteritis.* It must be recognised that intestinal disturbances and diarrhœa may be present without any definite catarrh, but in more severe cases there may be desquamation of the surface epithelium with other signs of inflammatory change—œdema, hæmorrhage, etc. We can thus speak of a desquamative catarrh. Such a change, which is attended by excessive formation of mucus, is seen in acute gastro-enteritis in children (a bacterial infection), and is a not uncommon complication in various fevers. In children, catarrh is often attended by swelling of the lymphoid follicles, the term *follicular enteritis* being applied, and in rare cases this may be followed by suppurative softening of the follicles and the formation of small ulcers. But it should be borne in mind that, apart from any inflammatory condition, the lymphoid tissue in children is often very prominent.

(B) *Croupous or 'Diphtheritic' Enteritis.* (The latter is merely a descriptive term, as the condition has nothing to do with diphtheria.) In this variety there is formation of false membrane composed of fibrinous exudate, usually along with a necrosed layer of the superficial part of the mucosa, the latter being involved to a varying degree. The membrane always appears first, and is most marked, over the summits of the folds of mucous membrane ; ulceration not infrequently follows. Such a condition is sometimes met with as a complication in acute infections, notably in puerperal cases ; it is the common lesion in bacillary dysentery (p. 560), and sometimes occurs as a secondary condition in cholera. This lesion may also be a complication in chronic affections, *e.g.* in uræmia where it may be associated with œdema and hæmorrhage ; we have seen it as a terminal occurrence in pernicious anæmia. Streptococci, coliform bacilli or other bacteria, are the causal organisms. In poisoning with corrosive sublimate there may be extensive membranous formation in the large intestine, and this is apparently a result of excretion of the poison through the wall of the colon. Lastly, in cases of retention of fæces especially above a stricture, the wall of the bowel, exposed to pressure and to bacterial action, may become the seat of a membranous enteritis.

(C) *Phlegmonous Enteritis.* This is a very rare condition, of nature similar to that described in connection with the stomach (p. 529). It is usually caused by streptococci, and the commonest site is the cæcum and ascending colon. The organisms gain access through some superficial lesion to the submucosa, where they spread and cause fibrinous or semi-purulent exudate. The exudate is visible as a yellow layer underneath the mucosa ; it causes thickening and stiffening of the wall and interferes with the peristalsis, so that symptoms of obstruction may result.

Ulceration of various kinds may occur in connection with these inflammatory lesions, the most important variety being in the large intestine—ulcerative colitis. The lesions which are met with in this condition resemble those met with in bacillary dysentery, but there may be no evidence that they are of dysenteric nature, their origin being often obscure. The ulcers, which may be large and numerous, run transversely to the gut, are of irregular shape and considerable areas of the mucosa may be destroyed. They may occur throughout the colon, but they are usually most numerous in the lower part and the rectum, and may be confined to these regions. Evidence of healing may be present at places and contraction of the lumen may result.

(D) *Mucous Enteritis or Colitis.* This form is to be distinguished from the previous, as the membranous structures which are passed by the bowel are composed merely of thickened mucus. The mucus collects in layers in the pouches of the colon and then becomes separated and discharged. On microscopical examination, the membrane-like structures are found to present a homogeneous mucoid material, in which are numerous bacteria but very few leucocytes. Mucous colitis is often a chronic and very intractable affection and is usually associated with depression and neurasthenia. Its causation is obscure, but it appears to be a condition of disordered secretion rather than of an inflammatory nature. In some cases the colitis has been accompanied by the presence of ' intestinal sand ' in the fæces—small gritty particles of lime salts, with admixture of pigment; such an occurrence is, however, very rare. It may be added that in constipation mucus is apt to accumulate around the fæces, and may be passed with them; such a condition disappears under treatment.

Acute Appendicitis. This lesion is of the highest importance on account of its comparative frequency and the serious results which often follow. The anatomical changes will be first considered, and thereafter the etiology will be discussed. The affection may be regarded as of three types. (*a*) It may be simply an acute inflammatory swelling; (*b*) it may have a suppurative or phlegmonous character; or, again, (*c*) it may be attended by gangrene—gangrenous appendicitis. The first two of these types may be regarded as different degrees of severity of the same condition; the third has special features of its own. Perforation may occur in both suppurative and gangrenous types.

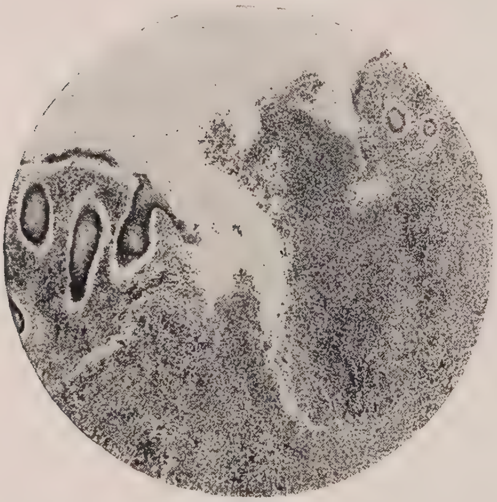

Fig. 345.—Acute Appendicitis, showing a local ulcerative Lesion in Mucosa with commencing Abscess formation beneath. (J. W. S. B.) × 60.

In the earlier stages of *acute appendicitis*, the appendix is found to be swollen, tense and markedly congested, and there may be a small quantity of lymph on the surface. When the appendix is cut into, the mucosa bulges owing to the swelling, and a certain amount of purulent-looking material may exude from the lumen. Such a condition is often spoken of as a ' catarrhal appendicitis,' but the term is not a suitable one, because the essential change in all forms is an *interstitial* inflammation; and we have never found evidence that catarrh of the lumen alone gives rise to the symptoms of acute appendicitis. On *microscopic examination* at this stage, one can usually find some focus situated at the foot of one of the indentations of the mucosa, where there is evidence of microbic infection and a varying degree of ulceration (Fig. 345). In other words, the infection is, in the first place, of a focal character, although there may be several foci. Around such a small lesion extension of inflammation into the other coats is found, and at a little later period the wall in its whole thickness may be seen to be overrun with leucocytes. At the same time inflammatory exudation is occurring from the blood vessels, increasing the swelling, and a thin fibrinous layer is often formed on the serous surface. The condition is thus an acute interstitial inflammation secondary to one or more focal lesions in the mucosa. We agree with Aschoff in considering that this mode of infection is of prime importance in the various types of appendicitis.

In other cases the changes are of greater severity. The inflammatory infiltration connected with the primary lesion may increase in intensity and lead to a small abscess in the wall, and this may give rise to a perforation. There may occur also a more general phlegmonous condition with foci of suppurative softening here and there, and even multiple perforations may be produced. This mode of perforation by intramural suppuration may take place quite apart from the presence of a concretion. When a concretion is present it may in some cases simply escape through such a perforation, but there is little doubt that when the concretion is of some size, the swollen wall will become stretched over it and the circulation in the wall will be interfered with, so that a perforation is liable to take place at that point.

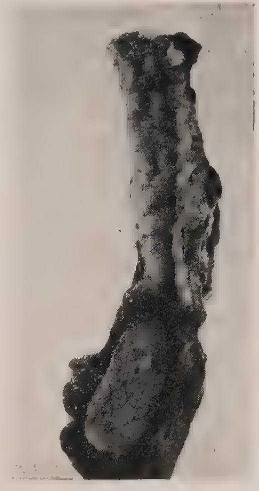
Fig. 346.—Acute Appendicitis. A concretion is lying in the distal extremity and the wall of the appendix around it is gangrenous.

Gangrenous Appendicitis. Gangrene may occur in the course of acute appendicitis. It then usually affects the distal portion, sometimes in relation to a concretion (Fig. 346) or it may occur in patches. In some cases it appears to be due to thrombosis of the veins in the meso-appendix, which, aided by the inflammatory condition, leads to hæmorrhage and stoppage of the circulation. But in other cases the gangrenous change appears at a very early period and affects the whole appendix apart from any vascular lesion. In such cases Wilkie considered that the two factors determining gangrene are obstruction at the outlet of the appendix and distension with fæcal material. He showed experimentally that a portion of closed small intestine filled with fæcal material becomes gangrenous within a short time, and general gangrene of the appendix may be produced in a similar way. The term ‘ acute appendicular obstruction' is now applied to such a condition and many cases of so-called fulminating appendicitis are of this nature. In any case of gangrenous appendicitis with or without perforation there is apt to occur an early general infection of the peritoneum; the organisms are of great variety, including anærobes.

The symptoms in gangrenous appendicitis are of sudden onset, there being vomiting and severe pain in the region of the appendix with rigidity of the abdominal wall; and an important fact is that, unlike what is found in ordinary acute appendicitis, temperature and pulse may be normal. This last fact may lead to the serious nature of the condition being overlooked.

Results. Acute appendicitis gives rise to important complications. In some cases there is merely a slight amount of fibrinous exudate on the surface, which does not spread and may afterwards give rise to local adhesions. In others, again, the condition goes on to suppuration, and a localised collection of pus may form around the appendix, which in many cases shows perforation or may be ulcerated across. Sometimes an escaped concretion is present in the pus. The suppuration may spread upwards along the cæcum and ascending colon and over the surface of the liver, or, again, pus may form in the pelvic cavity. Cases of this kind may run a course of considerable duration. In other cases, an acute general infection of the peritoneum may follow and a fatal peritonitis result. This is specially apt to occur at an early stage in gangrenous appendicitis. Other complications of appendicitis are due to infection of the veins. There may be a local septic phlebitis, and from this emboli may be carried to the liver, where they set up secondary abscesses. Again, a spreading thrombosis with secondary suppuration may extend up the portal vein—*pylephlebitis suppurativa* (p. 609).

Chronic Appendicitis. This usually is the result of an acute attack, though it may be of slight degree; sometimes there are several slight attacks. Chronic appendicitis is characterised by proliferative changes and increase of the connective tissue, and the changes may be mainly localised or of general distribution. A common result of a localised lesion of the appendix is obliteration of the lumen, and this may take place at one part of the tube, whilst elsewhere the mucosa may be comparatively well preserved. Such a condition may be readily understood in view of what we have stated with regard to the localised primary lesion. Again, as a sequel of the general acute interstitial inflammation, we may find a general fibrous thickening of the wall. In many cases, however, there is no history of acute attack and fibrosis apparently may result from chronic irritation When localised obliteration is present dilatation of the distal portion of the tube may follow (Fig. 347). This may be of slight degree, or there may be a cyst-like enlargement or *mucocele.* Another not uncommon result, owing to the distension acting on a localised lesion in the muscle, is the production of a diverticulum, which may project on the surface of the appendix. Occasionally rupture of a diverticulum takes place and its contents, which are generally of mucoid nature, may escape into the peritoneum ; reactive phenomena follow and the thick mucus is invaded by young connective tissue cells and by new blood vessels. Occasionally the mucus is in large quantities, and adhesions form with collections of mucus between. The microscopic appearances may simulate somewhat those of a mucoid carcinoma.

The effects of these fibrous changes vary. Sometimes there are no symptoms pointing to their presence, but on the other hand there may be slight attacks of intermittent pain in the region of the appendix, not infrequently accompanied by dyspepsia.

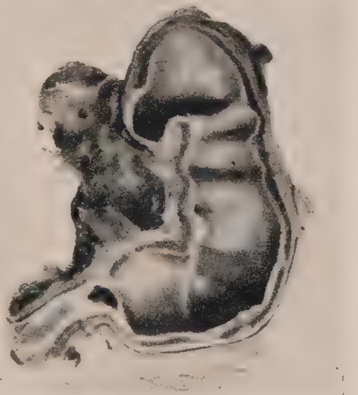
FIG. 347.—Chronic Appendicitis with obliteration at proximal end and dilatation of the distal portion.

ETIOLOGY. Although appendicitis is essentially a bacterial infection, there is still want of knowledge with regard to the particular conditions which lead to its occurrence. There is even doubt as to the organisms which primarily invade the tissues, although there is no doubt that the important effects are produced by coliform bacilli, streptococci and occasionally various anærobes ; some of the most virulent types are produced by streptococci. The view formerly held by some that appendicitis was produced by foreign bodies, such as cherry or date stones, etc., may be definitely discarded. Cases are recorded in which an irritating substance, such as a bristle or a pin, has been present, but this has no relation to the etiology of appendicitis in general. It is difficult to say exactly what part concretions play in appendicitis, and opinion on the subject varies greatly. These bodies, which vary in size and consistence, are essentially composed of fæcal remains and inspissated mucus, in which there is often deposition of lime salts. In some cases without inflammatory change an appendix contains fluid fæces, in others a cylinder of inspissated fæces, and, again, intermediate stages to ordinary concretions may be met with. But one can hardly suppose that concretions or fæcal collections aided by muscular movements and containing, as they do, an abundant bacterial flora, will always be without harmful result. We consider that they are a factor favouring infection, and that in addition they play an important part in gangrenous appendicitis, as has already been described. It must be admitted, however, that the factors determining the onset of appendicitis are imperfectly understood.

Diverticula and Diverticulitis. Diverticula are met with both in the small and large intestine, but they are much commoner in the latter. When fully formed they consist of protrusion of the mucous and submucous coats through the muscle of the wall and are thus often called 'false diverticula.' In the duodenum they may be single or multiple and the commonest situation is the inner aspect of the second part; they are comparatively rare. In the jejunum and ileum also they are rare, but when they are present they may be in considerable numbers. They are situated along the mesenteric attachment, projecting into the mesentery, and sometimes may reach the size of a walnut or even larger (Fig. 348). The contents of all these diverticula are fluid and symptoms rarely arise in connection with them. Though they are seldom met with before adult life, their origin is usually ascribed to congenital weakness of muscle which specially occurs at the site of entrance of arterial branches.

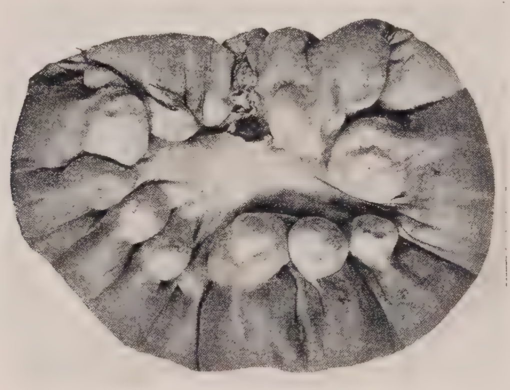

Fig. 348.—False Diverticula of small Intestine situated in mesenteric attachment.

In the colon, diverticula are comparatively frequent though they are present often without giving rise to symptoms. The lower portion of the colon is the commonest site, but they may occur at a high level. They may be in large numbers and may be situated on any part of the wall though rarely along the tæniæ coli. Small depressions at first, they enlarge and become spherical or flask-shaped, but they do not reach the size of those in the small intestine. They often contain inspissated fæces which may become hardened. The diverticula of the colon are regarded as essentially pulsion diverticula and are ascribed to such conditions as constipation, injudicious use of purgatives, irregular contraction of the bowel, etc. Occasionally, however, they may be associated with large diverticula of the small intestine which are not due to these causes. The condition of multiple diverticula is known as *diverticulosis.*

Inflammatory change, *diverticulitis*, usually of chronic nature, not infrequently becomes superadded. It affects the interior of the diverticula but, apparently due to toxic absorption, it leads to a general interstitial inflammation. Thus there is overgrowth of connective tissue throughout the wall and the lumen becomes narrowed and irregular. The narrowing may be considerable and localised, resembling carcinoma ; or it may affect a considerable segment of the bowel, which becomes stiffened. Acute changes sometimes follow or may occur at an earlier stage. There may be ulceration and perforation of a diverticulum containing inspissated fæces, localised abscess or diffuse peritonitis being the result. In cases of multiple diverticula the condition can usually be readily found on X-ray examination after barium administration. There is no evidence that carcinoma is apt to develop in connection with diverticula (Stewart).

SPECIFIC INFECTIONS

Quite a large number of inflammatory conditions of the intestines are produced by known organisms with definite characters, and they may be either acute or chronic in their course. The bacilli of the typhoid-coli group are the causal agents in an important group of such conditions. The typhoid and paratyphoid organisms affect chiefly the small intestine with special localisation in the lymphoid tissue. The food-poisoning bacilli (Gärtner's and others) cause acute catarrhal enteritis, especially of the small intestine, and the paratyphoid organisms sometimes have a similar effect ; while the dysentery bacilli affect chiefly the large intestine and cause both acute and chronic lesions. Other organisms which produce important effects are the cholera spirillum, the anthrax bacillus, actinomyces and the spirochæte of syphilis.

Typhoid Fever. Corresponding with the definite course of this fever there are inflammatory changes in the lymphoid tissue of the bowel, leading to destructive effects which may be followed by healing ; there is also a general catarrhal condition of the bowel.

The lesions are most marked in the Peyer's patches and solitary follicles in the lower part of the ileum, but the amount of bowel affected varies considerably in different cases. Sometimes the lesions extend for a considerable distance upwards ; on the other hand, we have seen them restricted to a few inches above the ileo-cæcal valve. As a rule, they diminish in severity from the valve upwards, and the higher ones may not pass beyond the stage of inflammatory swelling. The solitary follicles in the beginning of the large intestine are not infrequently affected, and the lymphoid tissue of the appendix also is sometimes involved. The different stages of the typhoid lesion are : (*a*) Acute inflammatory swelling of the lymphoid tissue followed by (*b*) necrosis ; then there occur (*c*) the separation of the dead tissue, with the formation of ulcers, and lastly (*d*) the process of healing. It may be said that, as a general rule, necrosis usually begins to be marked about the tenth day of the disease, and that the process of healing after the separation of the sloughs, begins about the end of the third week and may be complete in the fifth week; that is, in uncomplicated cases. The necrosis, however, does not affect all the inflamed lymphoid tissue; in parts resolution occurs without its so doing.

In the early stage the lymphoid tissue becomes swollen and prominent. The Peyer's patches are considerably raised and their surface comes to have a somewhat convoluted appearance, as parts are fixed by connective tissue bands, whilst the intervening portions swell. Necrosis then occurs irregularly in the inflamed patch and the swelling becomes more marked; the epithelium gives way and the process of ulceration starts. When this occurs the dead tissue imbibes the colouring matter of the bile and comes to have a yellowish brown and ultimately almost a black colour, though alterations in the effused blood also play a part in producing this appearance. Sometimes a whole Peyer's patch may be affected in this way, sometimes only a part (Fig. 349). The dead tissue gradually becomes separated and discharged by a process of ulcerative softening at the margin; an ulcer is thus produced. If the whole patch has sloughed, the ulcer corresponds to it in shape and extent; its margins are somewhat soft and shreddy, and when floated out in water are seen to be thin and undermined to some extent. Necrotic material may be seen on the floor, but if this has been cleared away the floor is comparatively smooth, and transverse markings due to the internal muscular coat may be visible.

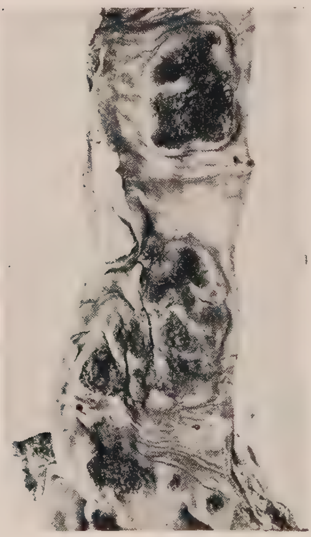

FIG. 349.—Lower end of small Intestine in Typhoid Fever, showing the necrotic change in the Peyer's Patches and solitary Glands.

The process of healing begins when the necrotic débris has been separated and the floor has been cleaned; columnar epithelium grows over the surface, and underneath it a layer of fibrous tissue forms. The lymphoid tissue and usually also the glands are not restored to any extent, but we have seen considerable new formation of the latter. At the site of a completely healed typhoid ulcer the surface has a smooth silky appearance and is often studded with minute pigmented points. An important point is there is never any tendency to cicatricial narrowing of the bowel. As can be readily understood from the comparatively rapid spread of the necrotic process, *perforation* is not uncommon, and general peritonitis, usually fatal, results. *Hæmorrhage* also, occasionally of considerable severity, may occur. In these respects there is a contrast to tuberculous ulceration, and the difference is due to the nature of the pathological processes in the two cases.

In the beginning of the *large intestine*, as has been said, the lymphoid follicles may be the seat of a similar lesion—they undergo marked swelling, become necrotic in the centre, and small rounded ulcers with swollen margin result (Fig. 350). When the *appendix* is involved the lesions vary in degree; sometimes they are of severe nature, there being considerable necrosis with the formation of brownish sloughs, and occasionally perforation follows. Here also the primary lesion is in the lymphoid tissue.

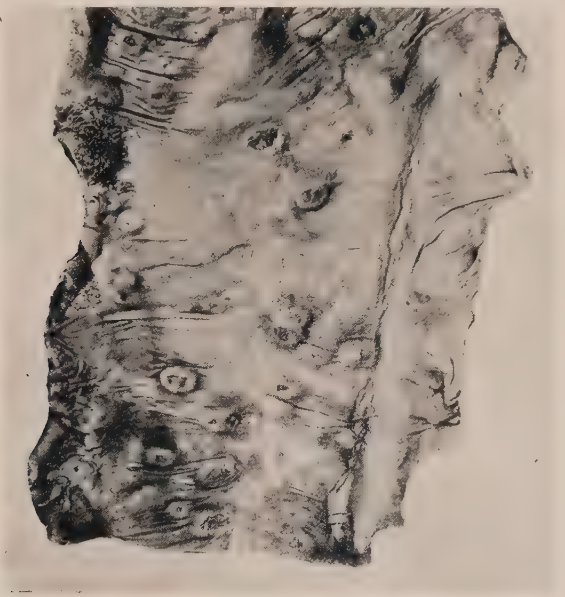

Fig. 350.—Large Intestine in Typhoid Fever, showing multiple small Ulcers.

The Histological Changes in the typhoid lesions are of a definite and somewhat characteristic nature. At an early stage, along with congestion there is a great increase of non-granular cells which are of various sizes. Some of these are derived from endothelial cells and also cells of the reticulum, which have become swollen and spherical. Others are monocytes and lymphocytes. Infiltration of similar cells may be seen extending along the lymphatics of the mucous and submucous coats for a considerable distance around, and also deep down in the muscular coats (Fig. 351). The great accumulation of such cells leads to the enlargement of the Peyer's patches, etc., and hæmorrhages occur and increase the swelling; there may also be some fibrinous exudate. There is little or no emigration of polymorpho-nuclear leucocytes to be seen in the affected area, but these cells may accumulate at the margin, especially when the dead tissue is in process of separation. The next stage is the occurrence of necrosis in patches and this gradually extends. The patches appear structureless and the cells have lost their nuclear staining, while there is often much karyorrhexis in the cells around, and many of the larger cells in the vicinity act as phagocytes and digest remains of cells and nuclei as well as red corpuscles. In the affected tissue, typhoid bacilli may be found in large numbers, and the necrosis is apparently due to their action, though thrombosis of small vessels also may play a part. In the superficial parts a variety of other bacteria from the bowel are present, and these increase in number and invade the dead tissue as necrosis becomes marked.

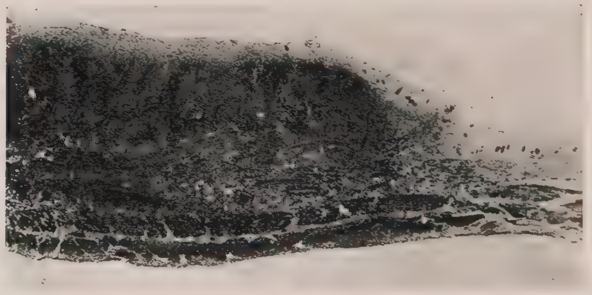

FIG. 351.—Margin of Peyer's Patch in early stage of Typhoid Fever, showing the marked inflammatory swelling. × 10.

The *mesenteric* glands undergo inflammatory swelling and may become greatly enlarged. At an early stage they have a pinkish colour and rather soft consistence, but later they acquire a greyish or even yellowish tint owing to the occurrence of necrosis, which may be attended by further softening. Their appearance, in fact, may be almost purulent, but true suppuration does not occur unless there is infection with other organisms. Occasionally a softened gland may rupture and give rise to peritonitis. The typhoid bacillus is present also in the glands, sometimes in large numbers.

Associated Lesions. The lesions which are met with in connection with typhoid fever throughout the body are of great variety, and may occur either during the disease or at a later period. They are referred to more fully in connection with the different systems, but a short summary may here be given with advantage. The comparative absence of emigration on the part of the polymorpho-nuclear leucocytes and the absence of the neutrophile reaction in the blood (p. 447) and bone-marrow are noteworthy features. In the enlarged spleen also there is an absence of the usual accumulation of polymorpho-nuclear leucocytes (p. 493).

In the production of lesions in other parts, two main factors are concerned, viz., absorption of toxins, that is, *toxæmia*, and the actual presence of typhoid bacilli in the blood, that is, *bacteriæmia*. In addition to the symptoms of fever, etc., toxic action is shown by the occurrence of cloudy swelling, which in the heart may reach a high degree and lead to cardiac weakness. In severe cases death may occur from heart failure, and this is due in part at least to the structural changes in the myocardium. We may mention also the occurrence of patchy necrosis of the abdominal muscles in typhoid, the so-called Zenker's degeneration, which is another evidence of toxic action. Catarrhal changes in the kidneys and inflammatory foci in the liver are due to the same cause, although, in the production of the latter, the actual presence of typhoid bacilli may be concerned (p. 600). Toxæmia has another very important effect, in that it causes a general lowering of the resistance of the tissues and leads to invasion by other bacteria. Thus laryngitis, bronchitis and pneumonic conditions, are of common occurrence. In the last mentioned, typhoid bacilli may be present along with pneumococci and other organisms.

The presence of organisms in the blood, with which the acute enlargement of the spleen is to be associated, may lead to infection of various parts. For example, the bacilli have been found in the rose-coloured spots which are often present in the skin in typhoid fever. The gall-bladder and the urinary tract often become the seat of bacterial growth with or without distinct inflammatory changes, and the bacilli may persist there for an indefinite time, producing the 'carrier' condition of the intestinal and urinary types respectively. At a later period calculi may form in the gall-bladder as the result of the bacterial invasion. Endocarditis, meningitis, or arthritis may be set up in the course of the blood infection, but they are comparatively rare. The periosteum of bones, and occasionally the perichondrium of the costal and laryngeal cartilages, may become the seat of inflammatory change. The ribs have a special liability to be affected by typhoid bacilli, and suppurative periostitis may occur several months after the attack of the disease ; occasionally it may recur in another part after operative treatment.

Paratyphoid Infections. The lesions met with in infections caused by the paratyphoid organisms, A and B, show considerable variations in their characters. Such infections were common in the war of 1914–18, paratyphoid B being the more frequent. In some cases the disease has the general characters of typhoid, though usually of milder degree, and the lesions have been found to correspond. There is a similar involvement of the lymphoid tissue, especially the Peyer's patches and solitary glands of the small intestine, with swelling of mesenteric glands, spleen, etc. ; but the necrotic and ulcerative processes are less marked and usually limited to a small part of the bowel. In other cases, however, a general acute catarrhal condition of the intestine is the characteristic feature and there is little implication of the lymphoid tissue; sometimes enteritis is associated with marked gastritis. It may be added that the 'carrier' condition may result from paratyphoid infections, as has been described above in the case of typhoid fever.

In infections with the *food-poisoning bacilli* the features present considerable variety, but, to speak generally, we may say that the chief lesion is an acute enteritis with intense swelling and congestion, and occasionally hæmorrhages; the small intestine is mainly affected, but the large intestine may be involved. The spleen is swollen and the bacilli in question can generally be obtained from it.

Dysentery. The term dysentery had originally a clinical significance and was applied to conditions of severe inflammation and ulceration of the colon, attended by frequent stools and tenesmus, and the passage of blood and mucus. Two main types of dysentery can now be distinguished on etiological grounds, namely, *bacillary* and *amœbic* dysentery; and the lesions of the two types also present important differences.

Bacillary Dysentery is produced by bacilli of the dysentery group, of which there are several varieties, distinguishable by their serum and fermentative reactions. The affection is essentially one of the colon, though the lower end of the ileum is affected in some cases, and it varies considerably in severity. In milder cases the lesion is mainly an intense catarrhal inflammation attended with much formation of mucus, œdema of the mucosa and hæmorrhage into it; but even in these there tends to be formation of fibrinous exudate on the summits of the folds of the mucous membrane. In the severer cases this change is more marked, and there is extensive membranous formation along with necrosis of the underlying mucosa. At first the false membrane appears in numerous small patches along the ridges of the mucosa and then the patches become confluent. This change is accompanied by the usual signs of intense inflammation with infiltration of polymorpho-nuclear leucocytes, escape of red corpuscles, etc. Leucocytes also pass in large numbers on to the surface and are present in the fæces mixed with blood and mucus; they can readily be found on microscopic examination of the stools, and this fact is sometimes of service in diagnosis. There follows separation of the dead tissue, with formation of ulcers, which begin over the ridges and then extend in an irregular manner, having a shreddy margin. In this way, large areas may become denuded of mucous membrane and the submucous layer becomes involved. In children the infection is often known as *acute ileo-colitis*; it is usually caused by bacilli of the Flexner and Sonne types. In the case of the former the lesions are usually more severe.

When the acute stage passes off, the process of healing may commence, but frequently the disease passes into a subacute or chronic stage, where attempts at healing and repeated ulceration occur side by side. When healing is effected, the ulcerated areas become covered over by epithelium and assume a comparatively smooth and even appearance; they thus present a contrast to the surviving mucosa, which is relatively raised, and in addition may show thickenings and even small polypoid growths. In chronic cases considerable contraction of the bowel may result. Owing to these changes the disease is often prolonged and relapses are fairly frequent. Bacillary dysentery may occasionally lead to pyogenic infection of the portal blood and suppuration in the liver, but the true ‘tropical abscess’ does not occur in this form.

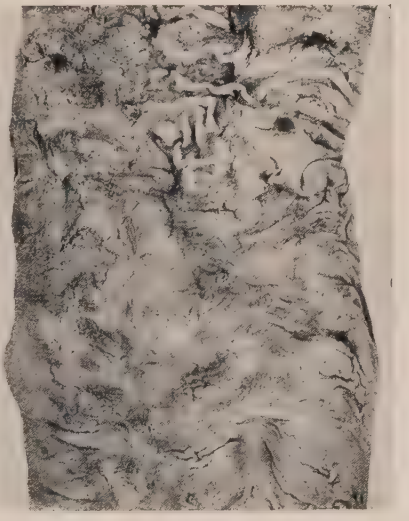

Fig. 352.—Portion of large Intestine in amœbic Dysentery at early stage before ulceration, showing the irregular swelling of the mucosa.

Amœbic Dysentery. This form is produced by the *Entamœba histolytica,* called also *Entamœba tetragena* owing to the formation of four cells in the cystic stage. The organisms, swallowed in the cystic stage in food or water, enter the wall of the large intestine through the mucosa and settle in the submucous tissue, leading first to an inflammatory œdema, which is attended by remarkably little leucocytic infiltration, and subsequently to necrosis of the tissues around them. They then spread in the submucous tissue and thus the necrotic process goes on. Accordingly, the first lesion visible to the naked eye is the formation of swollen congested patches in the mucosa, the central parts of which become soft and somewhat yellowish as necrosis occurs (Fig. 352). The mucosa then gives way and an ulcer is formed with shreddy and undermined margins. Such ulcers, as they spread, become confluent first in their deeper parts, so that a probe may be passed under the mucosa from one to the other; the bridges then give way and the ulcerated areas are greatly increased. Accordingly a considerable part of the bowel may have lost its mucosa, while in the intervening parts fragments of mucosa in process of disintegration and separation are present. Sometimes a gangrenous condition becomes superadded. The amœbæ are to be found at the margin of the ulcers, often in considerable numbers, chiefly in the submucous coat, but also extending more deeply

(Fig. 353). Occasionally they penetrate the small intestinal veins, and thus are not infrequently carried to the liver, where they produce tropical abscesses (p. 609). Sometimes in sections they may be actually seen within the blood vessels (Fig. 354).

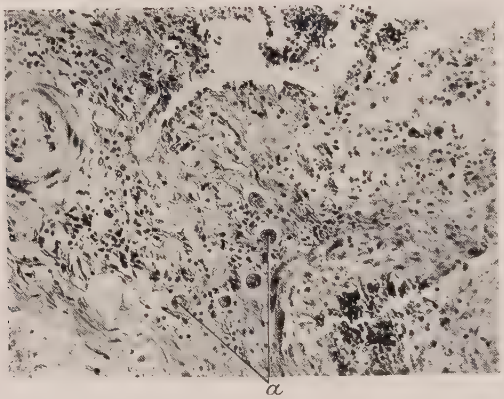

FIG. 353.—Section of Ulcer in amœbic Dysentery.
The entamœbæ (*a*) are seen as minute spheres scattered in the floor of the ulcer. × 100.

When the acute stage of amœboid dysentery has passed off, attempts at healing may occur. The necrotic tissue becomes thrown off and the epithelium grows over the denuded areas (Fig. 355). But the process is often interrupted, and, just as in bacillary dysentery, the disease becomes protracted or passes into a chronic condition. Overgrowth of fibrous tissue is apt to occur in the deeper coats with resulting narrowing of the bowel at places.

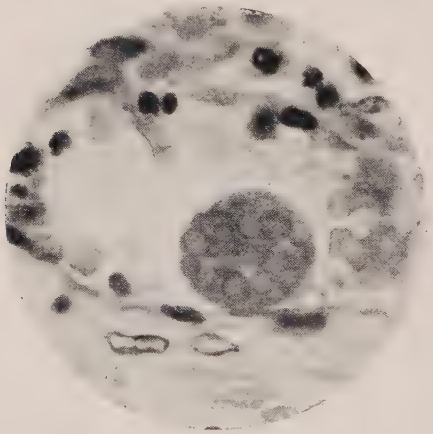

FIG. 354.—Blood vessel in floor of Ulcer in amœbic Dysentery; an Entamœba containing red corpuscles is seen in the interior. × 1,000.

Sprue. This is a chronic disease met with in India and other sub-tropical and tropical countries and is characterised by lesions and disturbance of the alimentary system. Glossitis, accompanied by rawness and redness of the surface of the tongue, is of common occurrence and may be followed by atrophy; vesicles and small ulcers also may be present. The stomach and intestines show marked atrophic changes. In a case on which I made a post-mortem examination, the intestinal walls were atrophied to an extent which I have never seen in any other condition. Achlorhydria is often, though not invariably, present and chronic diarrhœa is an outstanding feature. The watery stools contain a large amount of fat and have a markedly acid reaction. In association with these lesions, emaciation is often of marked degree. There is also anæmia and this may be of the megalocytic (hyperchromic) type (p. 460). The cause of the disease is still unknown.

Cholera. In this disease the primary lesion is an acute inflammatory infection, especially of the small intestine in its lower part, although there may be involvement also of the large intestine. The lesion is accompanied by intense congestion and by the formation of a very abundant watery secretion which contains little albumen. There is desquamation of the superficial epithelium and also of the upper parts of Lieberkühn's glands; and small shreds of epithelium become mixed with the fluid, giving rise to the 'rice-water stools.' The reaction is in response to the presence of the cholera vibrios, which occur in large numbers in the intestinal contents and also within the crypts of the mucosa. At a later stage there may be pseudo-membranous formation on the mucosa and even ulceration, but such a change is produced by the action of coliform and other organisms on the damaged wall. Although the vibrios are mainly confined to the intestine they may pass to the gall-bladder and other parts. A 'carrier' condition is sometimes met with, but it is usually of comparatively short duration.

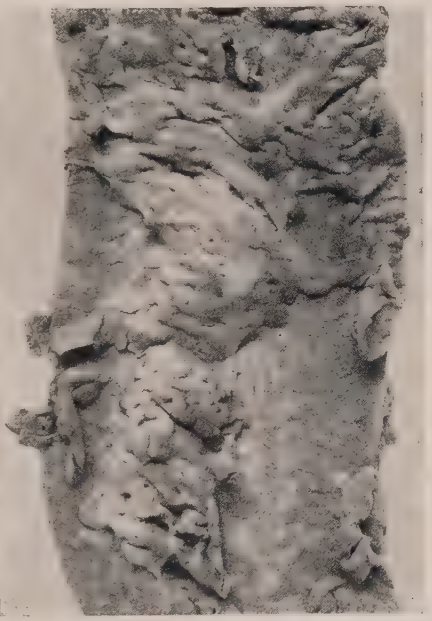

Fig. 355.—Large Intestine in chronic Dysentery (amœbic?), showing irregular smooth areas where the mucosa has been destroyed.

Anthrax. The intestinal infection by means of anthrax spores is comparatively rare in the human subject. It is to be noted, however, that this is the common mode by which the disease is transmitted in sheep and oxen. The site of infection is usually in the upper part of the small intestine and one or more focal lesions may be present. These appear as hæmorrhagic areas in the mucosa, and in the central parts there may be a paler and somewhat yellowish patch of necrosis. A considerable amount of œdema is present in the tissues around. On microscopic examination, the anthrax bacilli are often found in large numbers. From such a source general infection may result, and anthrax meningitis (p.738) occasionally occurs as a complication.

Tuberculosis. Two forms of tuberculous disease of the intestines are usually recognised, a *primary* and a *secondary*. *Primary infection* of the intestines is not uncommon in children as a result of the ingestion of cow's milk containing tubercle bacilli, but is very rare in adults. In children it often leads to extensive disease of the mesenteric glands—*tabes mesenterica*, but it is important to note that this condition may be produced by bacilli derived from the bowel without any visible ulcerative lesion to indicate the site of entrance. This probably means that the lesion has been minute and has not spread, rather than that the bacilli have been absorbed without producing any lesion.

The resulting disease of the mesenteric glands varies much in character. As has been mentioned, the glands may be enlarged generally and caseous, or, on the other hand, the affection may be localised. In the latter case, the disease may be arrested and fibrous encapsulation occur; and one occasionally finds in adults a few calcified lymphatic glands in the lower part of the mesentery, which represent the result of an intestinal infection in early life.

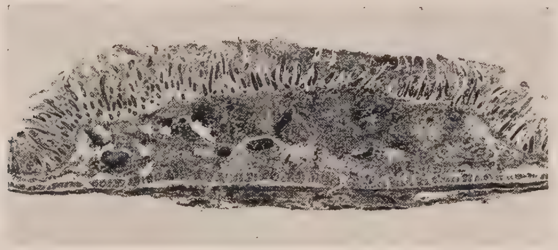

Fig. 356.—Early Tuberculous Lesion of small Intestine, showing formation of Tubercles in mucous and submucous coats. (G. H. W.)

The *secondary* type of intestinal tuberculosis is due to an infection of the bowel by tubercle bacilli in the sputum swallowed in cases of pulmonary tuberculosis; this is of common occurrence, being met with to some degree in the majority of cases of pulmonary phthisis. Ulcers are specially frequent in pulmonary tuberculosis in children. The small intestine is much oftener affected than the large, and the lesions usually start in the solitary lymphoid follicles and Peyer's patches. The bacilli there give rise to tubercles beneath the covering epithelium; these undergo caseation. The mucous membrane soon gives way and then small crateriform ulcers are formed. The disease spreads by direct extension of the bacilli around the small ulcer, and the new tubercles formed undergo ulceration in their turn. On *microscopic examination* the ulceration is seen to extend through the mucous into the submucous coat, whilst the muscular coat presents varying degrees of fibrosis with disappearance of the muscle fibres. Tubercle nodules are seen in the tissue beyond the margins of the ulcer, raising up the mucosa, and not infrequently they are present in the sub-serous layer (Figs. 356, 357).

In course of time ulcers of considerable size may be formed, and these tend to spread transversely to the line of the bowel ; sometimes, indeed, they encircle the gut (Fig. 358). The larger ulcers have an irregular outline, and their margins are raised and nodular, and not infrequently somewhat undermined. The floor is usually uneven or granular and may show caseous material but actual tubercles are rarely to be distinguished. The serous coat corresponding to the ulcer is often thickened and opaque, and an important point in aiding diagnosis is that tubercles may be visible in it and along the lines of the lymphatics draining the part. Tuberculous ulceration is rarely attended by hæmorrhage, and perforation is relatively uncommon ; in these respects there is a contrast to typhoid ulceration. The peritoneum may show various tuberculous lesions (p. 584) or merely chronic peritonitis.

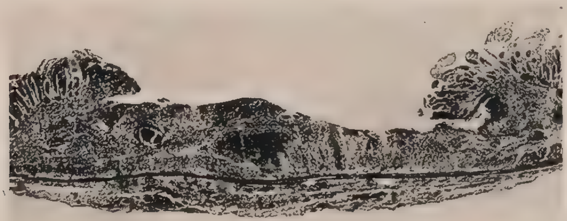

Fig. 357.—Small Tuberculous Ulcer of small Intestine with thickened and irregular margins and floor. (G. H. W.)

Tuberculous ulceration is less common in the *large intestine*, but sometimes one finds a few ulcers in it in cases of ulceration of the small intestine. There are besides two somewhat characteristic forms of tuberculous lesion. One of these is a localised tuberculous affection of the large bowel beyond the ileo-cæcal valve. The disease is of very chronic character, and leads not only to ulceration but to great thickening and contraction of the coats. In this way the lumen may be reduced to a narrow irregular channel and signs of intestinal obstruction may result (Fig. 359). The condition may involve the ascending colon for a distance of two or three inches, and the appearance of the lesion generally may

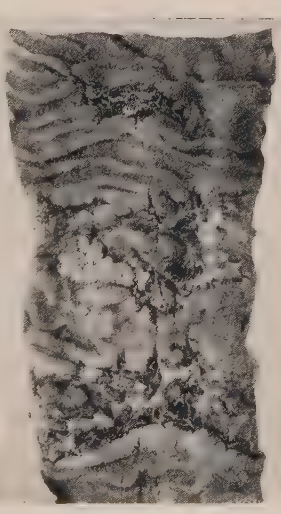

Fig. 358.—Tuberculous Ulceration of small Intestine.

Note the irregular character with transverse spread.

resemble that of a slowly growing carcinoma of the wall of the bowel. This lesion is sometimes known as 'tuberculous cæcal tumour.' Occasionally intestinal concretions form above a stricture, as may occur in other varieties; they are composed of inspissated fæcal remains with a varying admixture of lime salts.

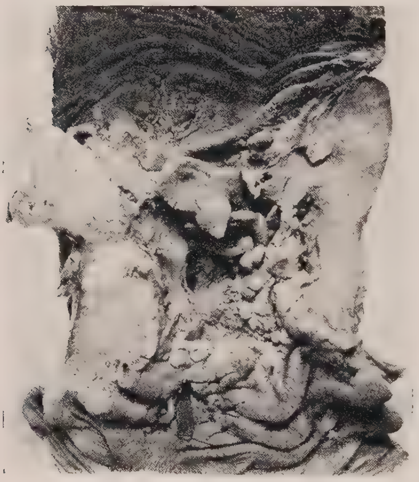

FIG. 359.—Chronic Tuberculosis of ascending Colon.

The lesion has produced great thickening of the wall with resulting obstruction. × ½.

The other type is a widespread ulceration which may affect a large part or almost the whole of the large intestine. Here also the disease is very chronic and the ulcers tend to spread around the bowel, and ultimately large areas of mucosa may be eaten away; the process is often attended by a considerable amount of fibrosis, and there may be contraction at places. Sometimes there are small polypoid excrescences at the margin of the ulcers. The origin of such a lesion is obscure. Local tuberculous disease occurs occasionally at the lower end of the rectum.

The *appendix* is not infrequently affected in cases of intestinal tuberculosis. The changes are of the usual kind. We may mention that we have sometimes found tubercle in appendices removed by operation, which were supposed to be the seat simply of chronic appendicitis, and this has been the experience of others. In some such cases there has been evidence of tuberculous disease elsewhere, but in others the patients have otherwise appeared healthy and the existence of tuberculosis has not been suspected. One cannot say whether the lesion in the appendix in such cases is to be regarded as of primary nature, but the possibility of this cannot be excluded.

Regional Ileitis. This is a condition which has been recognised only within the last few years. It corresponds to a specific infection though no causal agent has been found. The part of ileum affected is in the vast majority of cases the terminal portion, which is usually involved for a distance of eight or nine inches, though sometimes considerably more (Fig. 360). Occasionally there is affection also of the related part of the cæcum or the appendix. The lesion is essentially a thickening of the coats of the bowel, especially of the submucosa, due to œdema and inflammatory reaction. The lumen of the bowel is narrowed to a considerable extent owing to nodular swelling of its lining and thickening of its walls; a palpable cylindrical swelling often results. Ulceration follows in varying degree, and secondary infection leads to the usual inflammatory changes which may extend to the peritoneal coat. In these ways not infrequently there is chronic obstruction as a result, the degree of stenosis sometimes being great.

The earliest histological change would appear to be a hyperplasia of the lymphoid follicles attended by a marked œdema of the submucosa and lymphatic obstruction, infiltration of lymphocytes, etc. There then occurs in the majority of cases what may be regarded as a specific lesion, namely, the formation of giant-cell systems in the germ centres. These consist of accumulations of proliferating endothelial cells, often along with giant-cells of the Langhan's type. They are in short indistinguishable from tubercle follicles with the important exception that no caseation occurs. The secondary infection resulting from ulceration leads to the usual results—fistula, abscesses in the bowel wall, fibrosis, etc. The lesions in the lymph nodes are similar to those of primary nature in the intestine—hyperplasia of lymphoid tissue with formation of giant-cell systems. It will be seen that the lesions have a close resemblance to tuberculosis so far as structural changes are concerned. Tubercle bacilli, however, cannot be detected in the lesions and experimental inoculation from them has been attended with negative result. Further, the intestinal lesion has not been found to be associated with tuberculosis in other parts of the body. It is accordingly not possible to say anything definite as to the nature of the causal agent. It is quite possible that some cases of what are described as chronic tuberculosis of the ascending colon are of the same nature.

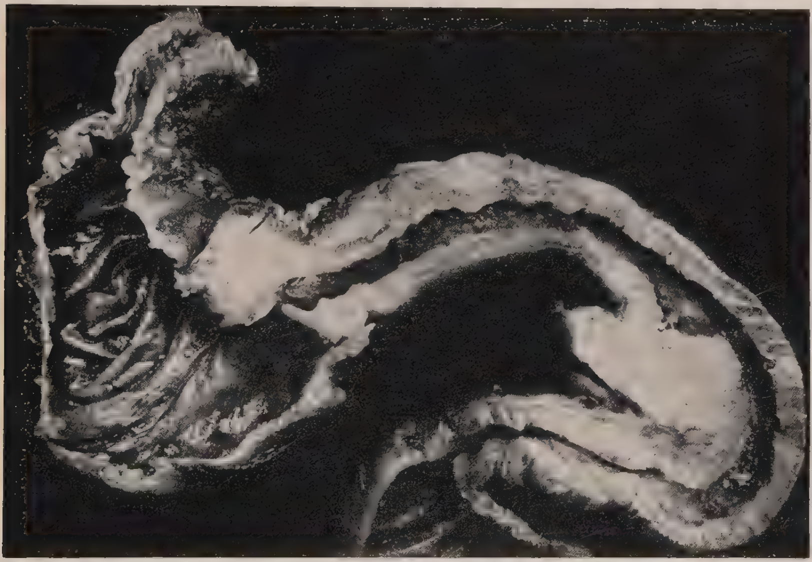

FIG. 360.—Regional Ileitis, showing diffuse thickening of wall of lower part of ileum with narrowing of its lumen. (Prof. G. Hadfield.)

Syphilis. In the tertiary stage of syphilis, lesions are sometimes present in the large intestine, the rectum being by far the commonest site. There is first formed a raised patch of gummatous infiltration in the mucosa and submucosa, which tends to spread transversely to the axis of the bowel. This undergoes ulceration and is attended, as elsewhere, by overgrowth of connective tissue and contraction. Ultimately the bowel may be involved in its whole circumference and stenosis may result, the condition sometimes simulating a malignant growth. In the case of the rectum, perforation from the ulcer is not uncommon, and suppuration may occur in the tissues around. Pus occasionally makes its way into the bladder, thus leading to the formation of fistulæ. Somewhat similar transverse lesions with ulceration have been described in connection with the small intestine, but this is a much rarer site. In the congenital type of the disease, multiple lesions are not infrequent, especially in the ileum. They are in the form of patches of inflammatory infiltration, which may undergo ulceration and resemble somewhat a tuberculous lesion. Sometimes the infiltration is of a more diffuse type, or, again, miliary gummata may occur. All these lesions show the usual histological features associated with syphilis.

Actinomycosis. As a path of entry to the parasite in this disease, the intestine comes next in order of frequency to the region of the mouth. The lesions are in connection with the large intestine, and sometimes ulcers with purulent infiltration of the submucous coat have been present; but in the great majority of cases the chief lesions have been outside the wall. The region of the cæcum is the commonest situation, although the disease has been met with in the tissues around the rectum. In a considerable proportion of cases, the parasite seems to gain entrance to the appendix, from which it may spread into the tissues around and give rise to an inflammatory mass of tissue which are areas of suppuration. It may pass also to the peritoneum and cause loculated collections of pus between the coils of intestine, and the pus may ulcerate through the wall of the bowel. Diagnosis can usually be readily made by the finding of colonies of the streptothrix on microscopic examination. Secondary actinomycotic abscesses (p. 383) not uncommonly occur in the liver, and suppurative pylephlebitis due to secondary invasion by other pyogenic organisms has been recorded.

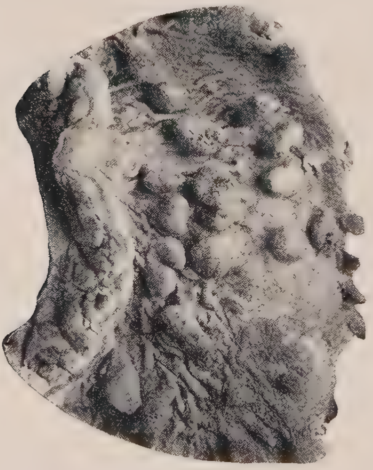

FIG. 361.—Bilharziasis of large Intestine, showing multiple polypoid nodules projecting from mucous surface. × ½.

Intestinal Bilharziasis or Schistosomiasis. This affection, which is met with in Egypt and other subtropical countries, is produced by the diœcious trematode, the *Schistosoma mansoni*, which is described below (p. 705). At present it is sufficient to state that the adult parasites lodge in the branches of the portal vein, especially the inferior mesenteric veins, and the females there lay ova which escape into the surrounding tissues. The ova give rise to much irritation and lead to lesions in the large intestine, especially in the rectum, of nature corresponding to those caused in the bladder by the *Schistosoma hœmatobium.* The eggs are oval in form, measuring about 140 μ in the long diameter, and have a small lateral spine near one extremity (Fig. 363, *b*). The lesions are of inflammatory nature and lead to general thickening of the mucous and submucous coats, and usually there are also nodular thickenings which enlarge and give rise to polypoid projections (Fig. 361). Ulceration with hæmorrhage occurs, and sometimes there is a considerable amount of fibrous thickening of the wall. The ova are present in large numbers in the lesions, where some of them are not infrequently calcified, and are to be found also in the fæces. The lesions tend to be specially marked in the descending colon and rectum, and thus symptoms like those of chronic dysentery result; the rectum may sometimes become prolapsed and the polypoid masses extruded. Cirrhosis of the liver (p. 608) is sometimes met with and is produced by the actual presence of ova; these may occur also in the lungs and other parts of the body. Unlike the vesical type intestinal bilharziasis does not appear to predispose to the development of carcinoma (Stewart).

MECHANICAL INTERFERENCES WITH THE INTESTINES

Intestinal Obstruction. Interference with the passage of the intestinal contents may be brought about in a variety of ways. It may be complete or incomplete, slowly or suddenly produced, and it may occur in the small or in the large intestine. We may add that sudden obstruction is met with especially in the small intestine, whereas obstruction in the large intestine is usually of a more gradual kind. The following are the chief *mechanical* causes of intestinal obstruction, which is known also as *ileus* :—

(A) Actual *obstruction of the lumen.* This may result from impaction of a large gall-stone which has ulcerated into the bowel, though spastic contraction of the bowel is here also concerned, as the stone may not be of a size sufficient to block the bowel completely. It may be produced also by the growth of a tumour into the lumen, usually a malignant tumour but sometimes a simple polypus. Not infrequently chronic obstruction is caused by fæcal accumulation.

(B) *Stenosis* caused by thickening and contraction of the wall usually takes place in the large intestine and is produced by such conditions as scirrhous carcinoma or a cicatrising ulcer, e.g. syphilitic or dysenteric. The obstruction from this cause is ordinarily chronic, but an acute state may be added. In the case of the small intestine, obstruction may result from an ingrowth of cancer from the peritoneal aspect.

(C) *Constriction* from outside—for example, by a hernial sac, by special conditions such as volvulus, intussusception, etc., or by fibrous bands. This is the commonest cause of acute mechanical obstruction.

(D) *Pressure from outside*, e.g. by a large tumour in the pelvis; obstruction is not often complete from such a cause.

The *effects of obstruction* vary greatly according to its position and degree, but we may describe as examples an acute obstruction of the small intestine and a chronic obstruction of the large intestine. When a portion of the small intestine is suddenly obstructed, e.g. by a fibrous band, the part above contracts actively and then passes into a condition of paralytic distension. There are probably both increased secretion from the wall and diminished absorption, and thus the bowel becomes distended with fluid contents in which there is abundant growth of bacteria. The fluid vomited, which is often in large amount, has corresponding characters. At first it is of clear character and is mainly gastric secretion ; it then becomes coloured owing to admixture with bile and ultimately brown and foul-smelling, often described as fæcal or stercoraceous. Loss of gastric secretion with hydrochloric acid and chlorides has important effects. It leads to a condition of *dehydration* ; the blood volume becomes diminished and the number of red corpuscles per c.mm. is raised. There is a fall in the blood chlorides which is reflected in a decreased excretion of chlorides in the urine ; ultimately they may be absent. The last occurrence is of great clinical importance. The blood urea often rises towards the end. Owing to the loss of chlorine ions the CO_2-combining power of the blood is increased, that is, there is a condition of alkalosis. Death is preceded by collapse. There has been much difference of opinion as to the mode of production of symptoms. By some they have been referred mainly to toxic action, the poisons being produced either by bacteria or being the result of breakdown of tissue proteins. Others again consider that the symptoms depend upon the dehydration with alkalosis. It has been abundantly established, however, that the hypochlorhydria is of special importance and also that the life of animals with acute obstruction can be prolonged by the injection of sodium chloride solution intravenously or into the bowel below the obstruction. If nutrient substances be added to the saline they can be kept alive for a considerable time.

The above account refers to the effects of mechanical obstruction of the small intestine, especially when it is at a high level, but when there is also *strangulation* other factors come into play. The effect then varies with the amount of bowel strangulated, but when this is of moderate length action of toxins plays an important part ; the peritoneal exudate has been found to have distinctly toxic properties. Of course, there is often peritonitis in addition, as a result of penetration of the wall by bacteria ; the symptoms are then produced in the usual way. The state of strangulation is more fully described below in connection with some of the conditions which produce it.

In addition to these mechanical causes, what amounts to obstruction may be produced by sudden atony of the muscular coats, this being known as the *paralytic* or *adynamic form of ileus*. It occurs sometimes after operations, from mechanical handling of the intestines, and sometimes the term is restricted to this form. The symptoms are of all degrees of severity and may resemble those which have been described as occurring in acute mechanical obstruction. The ileus so common in peritonitis also results from paralysis of the muscle, though it is brought about in a different way. This type of obstruction is produced when the blood supply is cut off, e.g. by plugging of the superior mesenteric artery, and also when a portion of the bowel is diffusely and intensely inflamed, e.g. in phlegmonous enteritis.

In the case of a partial *chronic obstruction of the large intestine*, the wall above, in addition to becoming distended with fæces, undergoes hypertrophy in a varying degree. The pressure of the fæcal accumulation on the distended wall interferes with the blood supply and impairs the nutrition, and hence bacterial invasion may occur and an exudate may form on the mucous surface. In other cases the stretched mucosa gives way and so-called 'fæcal ulcers' form. Perforation of such an ulcer may occur, and hence it happens that sometimes in a case of chronic stricture the perforation may be at some distance above the obstruction. The large intestine tolerates obstruction much better than the small intestine, and chronic stricture may lead to complete obstruction for some days with comparatively slight symptoms.

Hernia. The term really means a rupture, but it is applied to any protrusion of a portion of viscus outside its natural cavity. In the case of the bowel, the protrusion usually occurs in a pouch of the peritoneum, and this in most instances projects on the surface of the body, forming an *external hernia* ; in rare instances the peritoneal layer becomes ruptured. The term *internal hernia* is applied when there is no swelling present outside. In the occurrence of hernia two prime factors are concerned, viz. (*a*) *local weakness* and (*b*) *increased pressure*, the latter being usually brought about by muscular exertion, coughing, straining at stool, etc. The local weakness is often (probably as a rule) of congenital origin, and it is clearly so in certain sites, e.g. at the umbilicus or the inguinal canal ; occasionally it results from the stretching of the scar of an operation wound.

Of the *external* types of hernia, the commonest are the *inguinal*, *femoral*, and *umbilical*. Others less common, are the *ventral*—through any portion of the abdominal wall other than the sites mentioned—*obturator*, etc. The inguinal herniæ are of two varieties, the indirect, where the hernia follows the inguinal canal outside the deep epigastric artery, and the direct, which passes internal to the latter vessel and comes through the external abdominal ring. The femoral hernia passes under Poupart's ligament internally to the femoral vessels. Examples of *internal* hernia are seen when the protrusion occurs through an aperture in the diaphragm, through the foramen of Winslow, or into a pouch in the jejuno-duodenal fossa, the pouch then passing behind the peritoneum. In the ordinary external herniæ, the contents are usually a portion of small intestine, though in the larger ones omentum or other structures may be present. Whilst it is generally possible to return the contents into the abdominal cavity, the hernia then being termed 'reducible,' this may be impossible owing either to the bulk of the contents or to adhesions which have formed.

The most serious results of hernia are those of strangulation and are seen when the conditions are such as to interfere with the circulation in the protruded bowel. This may occur by the addition of a fresh piece of bowel to the sac or by accumulation of fæces and gas. Sometimes it happens when the hernia is first formed, a portion of bowel being forced into a tight aperture; this is not uncommon in the case of femoral hernia. The changes following strangulation have already been described (p. 22). Along with the strangulation, obstruction also is, of course, produced when the bowel in its whole thickness is involved. This in fact may occur apart from strangulation.

Intussusception. This is a condition in which one portion of the bowel is pushed down or invaginated into the portion below. Such an occurrence not infrequently takes place in the small intestine in children at the time of death, owing to irregular contractions of the bowel, and the term *agony intussusception* is applied to it. Several intussusceptions may be present. In this form the portion of bowel invaginated may be readily removed and there is no marked congestion or indication of interference with the blood supply; the condition is accordingly of no practical importance.

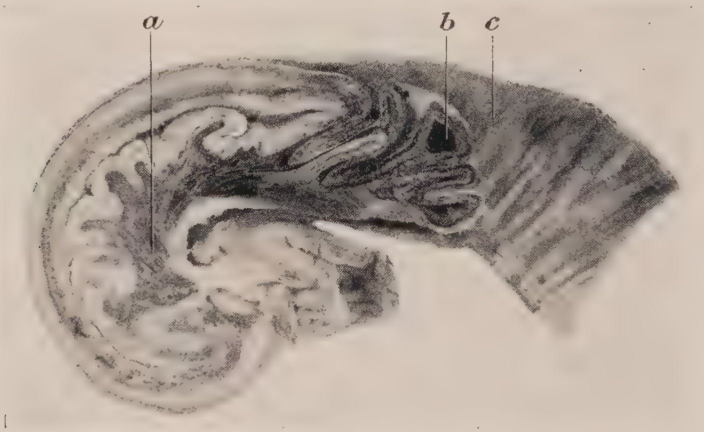

FIG. 362.—Longitudinal Section of Ileo-cæcal Intussusception.
(*a*) Mesentery drawn in and hæmorrhagic, (*b*) apex of intussusception, and (*c*) colon. (J. W. S. B.) × ⅔.

Intussusception may, however, occur in a condition of health and lead to very serious results; here again it is met with chiefly in children. The commonest site is at the ileo-cæcal valve, and usually the valve forms the apex of the intussusception and is passed along the large intestine (Fig. 362). The apex may ultimately reach the rectum, and when this happens, the bowel affected forms a fairly firm sausage-shaped mass, which is palpable during life. This type of intussusception is called *ileo-cæcal*. More rarely the small intestine is passed through the orifice into the colon—*ileo-colic* type,—and there may be also combinations of these two types with more complicated arrangements of the parts. For example, the ileo-cæcal valve may be passed along for only a short distance, so that the tip of the appendix may be still visible, and then through the upper opening coils of the small intestine may be passed down and firmly impacted. Intussusception occurs in other situations, for example, in the small intestine or the transverse colon, but it is comparatively rare. It occurs sometimes in connection with a polypus, over which apparently the intestine contracts and which it then endeavours to pass along as if it were a foreign body. The intestinal wall at the site of attachment is thus drawn in and intussusception results. In intussusception of the ordinary type three layers of bowel are to be seen on section, viz. two layers formed by the doubling of the bowel invaginated, and one layer constituted by the wall of the bowel into which the intussusception has occurred; but, as has been stated above, a more complicated disposition of the bowel may be present. Intussusception of the appendix has been recorded, but it is very rare; it occurs chiefly in children.

RESULTS. The important effect of intussusception is due to interference with the blood supply. The vessels of the invaginated part are pulled upon and also constricted; intense venous engorgement is the result, and this is followed by diffuse hæmorrhage into the tissues of the bowel. Accordingly the passage *per anum* of a mixture of blood and mucus, compared to red-currant jelly, is a common sign of intussusception; often pure blood is passed. Following upon the hæmorrhagic infarction of the bowel, necrosis may take place and the part undergo gangrenous softening. It will be noted that, at the upper part of the intussusception, the serous surface of the invaginated part is in contact with that of the bowel receiving the invagination, and thus at this point adhesions may form and prevent extension of organisms to the peritoneum. The dead tissue of the invaginated bowel may gradually slough away and a process of natural cure follow. In other cases, however, death may occur from general toxæmia, or organisms may gain access to the peritoneum and cause a diffuse peritonitis. When a favourable result follows without operation, portions of sloughs from the dead bowel may be passed for a considerable time after the intussusception has occurred.

Volvulus. This is a condition in which a loop of bowel is twisted or rotated through two right angles or more, so that obstruction and a varying degree of strangulation result. The condition is most apt to occur when a loop has a long attachment and the ends are comparatively close together, rotation in such cases being, of course, facilitated. The great majority of cases are met with at the sigmoid flexure, and the occurrence of the volvulus is aided by a long mesocolon and by a loaded condition of the sigmoid due to constipation. Usually the upper part of the sigmoid passes forwards and downwards so as to lie in front of the upper part of the rectum. Once the twist has occurred, passage of fæces is prevented. The bowel becomes more and more distended, the venous return is interfered with, and the wall becomes congested and hæmorrhagic ; ultimately it may become almost black. In some cases a portion of bowel is found to be enormously distended, filling a large part of the abdominal cavity. Volvulus of the small intestine may occur also, but it is less common ; the favouring conditions are the same, and sometimes the approximation of the ends of the loop is due to local adhesions. In children, however, volvulus of the small bowel is much commoner than in the adult. Occasionally two loops of intestine become intertwined and then the symptoms are very severe ; but such a condition is rare.

Hirschprung's Disease. This is a rare affection which is met with in the earlier years of life and is apparently of congenital origin. It is characterised by an enormous distension and enlargement of the colon which then forms a large proportion of the abdominal contents, and gives rise to great swelling from accumulation of fæces which may be voided only at considerable intervals. The whole of the large intestine may be involved, but sometimes mainly the lower part. As a rule the rectum is not involved in the distension, or is involved in less degree. In a considerable number of cases a kink or a valve-like arrangement has been present at its junction with the sigmoid, but this is now regarded as produced by the weight of the overloaded bowel above and not as the cause of the obstruction. The disease is considered to be in most cases the result of neuro-muscular inco-ordination. In this the main factor appears to be overaction of the sympathetic, the action of which normally is to inhibit the propulsive contraction of the intestinal wall and stimulate contraction of the internal anal sphincter. In accordance with this view, operation in the form of removal of the lumbar sympathetic trunks with their ganglia and communicating branches has been performed, this operation giving the motor nerves more control of the colon. In quite a number of cases favourable results have been obtained. The disease is now regarded as an example of *achalasia* and is put in the same category as other conditions in which there is neuro-muscular inco-ordination, *e.g.* œsophagectasia and congenital stenosis of the pylorus.

Cœliac Disease. This somewhat rare condition, which is met with in children, is characterised by marked deficiency in the absorption of fats from the bowel with resultant wasting and impairment of development—hence it is also known as intestinal infantilism. The fæces are greatly increased in bulk, pale, soft and foul-smelling, and contain a large amount of fatty material. Telfer has found that the fatty derivatives may be double the normal and that they are chiefly in the form of calcium soaps. There is, at the same time, diminished absorption from the bowel of inorganic constituents, calcium and phosphoric acid, and the urinary excretion of these is low. The deficiency in the absorption of iron, which is a distinct feature, is to be related to the anæmia which is usually present. Occasionally the anæmia is of the macrocytic or pernicious type. There is no deficiency in fat-splitting, and the essential change thus seems to be a failure to absorb fats with secondary loss of mineral matter. The condition was at one time said to be the result of enteritis, but in recent post-mortem examinations there has been found no evidence of this or other lesion, and the cause of the defect in absorption is unknown. The disease is known also as *idiopathic steatorrhœa* and *Gee's disease.*

Intestinal Parasites [1]

The commonest intestinal parasites are the two cestodes or tape-worms—*Tœnia mediocanellata* and *Tœnia solium*, and the three nematodes—the *Ascaris lumbricoides*, *Oxyuris vermicularis* and the *Trichocephalus dispar*. We shall mention only some of the main characters of these parasites. The *Ankylostoma duodenale* (*vide* p. 464) and the *Dibothriocephalus latus* (*vide* p. 460) are of importance in relation to their pathological effects. For an account of parasites occurring in the tropics, reference must be made to special works.

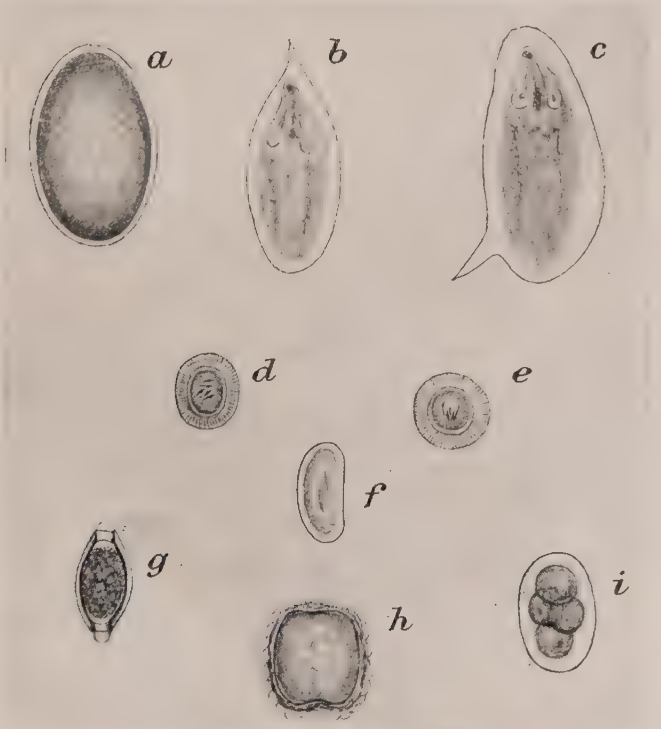

FIG. 363.—Eggs of Parasites :—

a, Fasciola hepatis or Distoma hepaticum ; *b*, Schistosoma hæmatobium ; *c*, Schistosoma mansoni ; *d*, Tænia saginata or mediocanellata ; *e*, Tænia solium ; *f*, Oxyuris vermicularis ; *g*, Trichocephalus Trichiurus or Trichocephalus dispar ; *h*, Ascaris lumbricoides ; *i*, Ankylostoma duodenale. (Rd. M.) × 200.

Tœnia mediocanellata or saginata. This tape-worm, which is the commonest in this country, is of large size, its length sometimes reaching eight yards or

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[1] For full details as to parasites, with references to literature, the student may be referred to *Animal Parasites of Man*, by Fantham, Stephens and Theobald, London, 1916, and *Précis de parasitologie*, by E. Brumpt, 5th edit., Paris, 1936.

more. The head or scolex is minute, measuring about 2 mm. across; it has four suckers, but neither a rostellum nor hooklets. The proglottids are numerous, sometimes as many as 1,000 being present. The genital pore is marginal, usually alternately placed in successive segments, and the uterus possesses from 20–30 lateral branches. The 'eggs,' which are to be seen in the fæces, are oval in form and about 30–40 μ in length and 20–30 μ in breadth (Fig. 363, *d*). The shell or embryonophore is radially striated and contains an embryo or oncosphere which possesses three pairs of spines. The bladder stage or cysticercus occurs in the muscles of the ox, and is in the form of minute oval cysts measuring about a third of an inch in the long axis. Infection of the human subject is caused by the ingestion of imperfectly cooked beef containing the cysticerci, the parasite thereafter attaining its full development in the intestine.

Tænia solium or T. armata. This parasite, though in this country less common than the preceding, is the commonest tape-worm infecting man. It is met with especially in countries where pork is consumed in an imperfectly cooked condition. The T. solium is of smaller size than the T. mediocanellata, its length rarely exceeding ten feet, whilst the proglottids are proportionately smaller. The scolex is of rounded form measuring about 1 mm. in diameter, and has four suckers and a rostellum, with about twenty-eight hooklets arranged in two rows. The genital pore is lateral and its position usually alternates in successive segments; the uterus possesses from 7–10 lateral branches. The ova are spherical or slightly oval and measure 30–36 μ in diameter (Fig. 363, *e*). Like that of T. mediocanellata the embryonophore or shell shows radial markings and contains a six-hooked oncosphere. The larva stage—*Cysticercus cellulosæ*—occurs chiefly in the intra-muscular tissue and in the organs of the pig, giving rise in the former to the condition known as 'measly pork.' When such pork is eaten without being heated to a temperature sufficient to destroy the parasite, the scolex lodges in the intestine, where it produces proglottids and reaches full maturity. It is to be noted, however, that in some cases cysticerci of the T. solium have been met with in the human subject, especially in the superficial parts of the brain and in the eye, and also in voluntary muscle.

Other tape-worms have occasionally been found in the human subject, for example the T. canina or T. cucumerina, which is a small tape-worm of less than a foot in length, and common in the dog and cat. Such forms are rare and of little importance.

Ascaris lumbricoides. This is the common 'round worm' and resembles somewhat an earthworm in appearance. The female measures about 25 cm. or even more in length, by about 0·6 cm. in thickness, whilst the male is somewhat smaller. The eggs, which may be found in large numbers in the fæces, measure about 65 μ by 50 μ (Fig. 363, *h*). They are oval or somewhat barrel-shaped, and the outer surface is rough or mammillated in appearance; within each a somewhat granular ovum is seen. Outside the body the embryo undergoes development up to a certain point within the shell. The ova have considerable powers of resistance, and infection occurs by swallowing the eggs; the shells are dissolved by the gastric juice and the larvæ are set free. The larvæ then bore their way to various parts, especially the lungs where they may produce pulmonary symptoms. Later they ascend the trachæ and pass to the intestine where they reach maturity. The normal habitat is the upper part of the small intestine, but occasionally a worm may wander into the stomach or œsophagus, or into the common bile-duct and lead to obstruction. Cases are known where an ascaris has ascended into the nasal cavity or passed into the larynx. Perforation of the bowel by an ascaris with the production of peritonitis has been recorded. The presence of round worms may be attended by few or no symptoms, but sometimes, especially when they are numerous, malnutrition and intestinal symptoms—colicky pains, vomiting, etc.—may result; and not infrequently they give rise to nervous symptoms by reflex irritation.

Oxyuris vermicularis. This is a small nematode worm usually known as the 'thread-worm' from its appearance. The females measure about 10 mm.

in length and about 0·5 mm. in thickness ; in the fæces they appear like wriggling pieces of white thread. The males are of about half the length of the females and proportionately thinner ; they are accordingly more difficult to find. The worms inhabit chiefly the cæcum but occur also in the lower part of the small intestine ; the females, when mature, descend to the rectum where they lay their eggs They wander from the anus, especially at night, and spread over the skin to adjacent parts, passing sometimes into the vagina and even into the body of the uterus. The eggs are deposited in these situations and intense irritation is produced. The eggs are oval in form, thin-shelled and flattened on one side and measure about 50 μ in length and 20–25 μ in breadth (Fig. 363, *f*) ; each contains a folded tadpole-like embryo in the interior. There is no intermediate host and infection occurs by swallowing the eggs. It can be easily understood that a child, after scratching the irritated parts, may readily transfer the eggs to the mouth. Sometimes the thread-worms may be present in enormous numbers, and give rise to symptoms of intestinal irritation and not infrequently to reflex nervous phenomena. They are common in the appendices of children.

Trichocephalus dispar or Trichocephalus trichiurus. This parasite is of common occurrence and is ordinarily known as the ‘ whip-worm.’ The term is applied on account of its form, the posterior part being thicker than the anterior, which is thin and filamentous. The female measures about 45 mm. in length, the thicker posterior part being comparatively straight ; the male is a little smaller, while the posterior part is coiled up in a spiral-like manner. The eggs, which are to be found in the fæces, are oval in form and of brownish colour, measuring about 50 μ by 25 μ. They are distinguished by the presence of a small body at each pole, which acts as a sort of plug to a deficiency in the shell (Fig. 363, *g*). Within the latter there is an unsegmented ovum. Outside the body the eggs have great powers of resistance, as in the case of those of *Ascaris lumbricoides* ; the embryos gradually develop and infection takes place by swallowing the eggs, the embryos being set free by digestion of the shells in the stomach. No intermediate host is necessary. This parasite inhabits especially the cæcum and ascending colon ; it is not infrequently present in the appendix, where it appears to do little harm. The worms are said to become attached to the wall by penetrating the mucous membrane by means of the filiform anterior end. This parasite is of widespread distribution and is very common in certain districts. It is usually regarded as practically innocuous, and although nervous symptoms have been ascribed to it, it may be present in large numbers without any recognisable effects.

TUMOURS

The tumours of the intestine may be said to correspond in a general way with those of the stomach. Thus *neuro-fibroma*, *leiomyoma*, and *lipoma* are met with, though rarely. Both myoma and lipoma may be either subserous or submucous in position, and a subserous myoma may reach a large size. The commonest simple tumour, as in the case of the stomach, is the *papilloma* or *polypoid adenoma*. It may be single and may reach a considerable size, and may give rise to intussusception (p. 572). In certain cases the growths are multiple, and occasionally in considerable numbers throughout the intestines. Polypoid growths may be found sometimes as a sequel to inflammatory and ulcerative conditions, e.g. chronic dysentery and tuberculosis, but often there is no evidence that they have occurred secondarily to an inflammatory lesion. Occasionally they are associated with polypi of the stomach. Sometimes carcinoma develops in connection with a simple papilloma. Recent statistics show, in fact, that such an occurrence is comparatively common. For instance, Stewart found that in 28 per cent. of cases of carcinoma of the colon there was an association with one polypus or more. The relation to cancer is, however, more distinctly seen in the condition called *polyposis intestini*, which is characterised not only by the large number of papillomata present, but also by the fact that it is an abnormality of familial nature. In a number of cases it has been also clearly shown that it is hereditary, the predisposition being a Mendelian dominant. In *polyposis intestini* the ultimate development of carcinoma is of very frequent occurrence. Polypoid adenomatous growths are not infrequently found in the rectum in children. Sometimes *angioma* is found in the intestine and may be multiple.

Of the malignant growths *carcinoma* is by far the commonest. In the small intestine, it sometimes starts at the papilla of Vater, but apart from this situation, primary carcinoma is extremely rare. In the large intestine it is relatively frequent ; the commonest site of all is the upper part of the rectum, while the flexures and the region of the ileo-cæcal valve come next. The chief forms may be said to be the scirrhous or contracting form, the soft or encephaloid, and the mucoid or colloid. In the great majority of cases the tumour is of the type of an adeno-carcinoma, but occasionally the cells are irregularly arranged. The more slowly growing types have a great tendency to encircle the bowel, forming a ring-shaped growth and thus producing narrowing or, it may be, complete obstruction. The bowel above the obstruction undergoes great, sometimes enormous dilatation, while its wall becomes hypertrophied (Fig. 364). The pressure of the contained fæces interferes with the nourishment of the mucosa and a pseudo-membranous inflammation may be super-

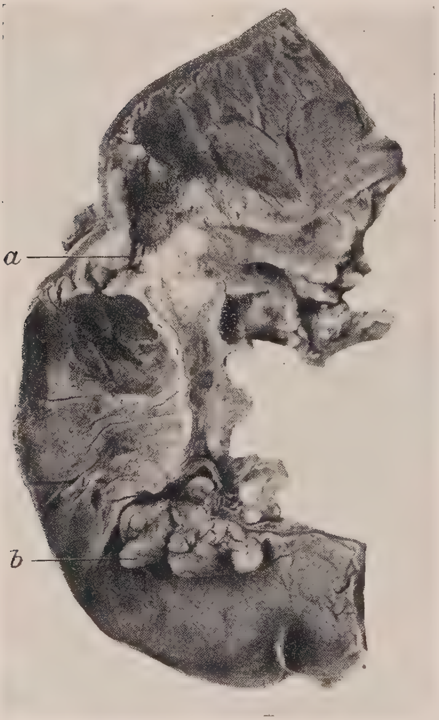

FIG. 364.—Cancerous Stricture (*a*) of Colon.

Note the hypertrophy of the wall above ; below there is a simple pedunculated adenoma (*b*).

added. In other cases, the wall becomes thinned and a so-called fæcal ulcer may follow, and this may undergo perforation with resulting peritonitis. The softer type of cancer forms an irregular mass which in its turn may bring about obstruction by projecting into the lumen (Fig. 365). The mucoid type may, as in the stomach, lead to widespread infiltration and thickening of the wall, and may give rise to secondary growths in the peritoneum. It is of interest to note that this type of cancer is not very uncommon in the earlier years of adult life. In cases of cancer, invasion of the lymphatics takes place at an early period, but secondary growths in the liver usually occur late or not at all. The growth occasionally spreads to the peritoneum, and results similar to those described in the case of the stomach are produced. The most important precancerous condition is the presence of intestinal papillomata just described above. Squamous epithelioma may occur in the mucosa of the anal canal.

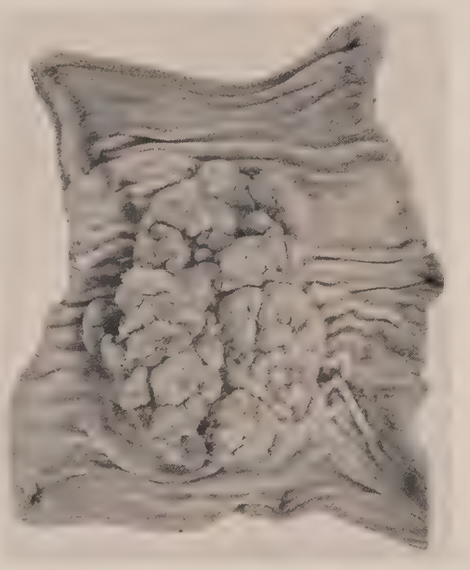

Fig. 365.—Large Fungating Adeno-Carcinoma of descending Colon. × $\frac{2}{3}$.

True carcinoma may originate in the *appendix*, but this is very rare. A less uncommon type of growth, however, occurs as a small nodule usually situated towards the free extremity, and presenting an alveolar structure like a cancer. It is known as a *carcinoid*. The growth, which has a brownish-yellow colour owing to lipoids in the cells, is usually not larger than a pea, often smaller, and it is not uncommon to find accidentally small collections of similar cells on microscopic examination of appendices.

The cells are somewhat small and are irregularly arranged in closely packed masses in the submucous coat, though extending into the other coats (Fig. 366). In cases of this condition which we have seen, we have found no evidence whatever of active growth, and this has been the general experience; in a few cases, however, metastases have been observed. A similar form of tumour occasionally occurs in the wall of the small intestine, where it is usually multiple. Most of the malignant examples have been in this situation. Masson has shown that the cells contain minute granules which reduce silver salts—hence called ‘argentaffine cells.’ In this respect they correspond with the cells of Kultschitzky, which occur at the bottom of the crypts of Lieberkühn and which are believed by some to have an endocrine function. Some of the cells in the carcinoid tumours resemble these cells also in form, and Masson considers that the tumours take origin from them and are related to nerves. He accordingly speaks of the growths as ‘endocrine adenomas.’ In the case of the appendix the occurrence of carcinoid tumours has been found to be related to old inflammatory lesions. A carcinoid growth is also known as an *argentaffinoma*.

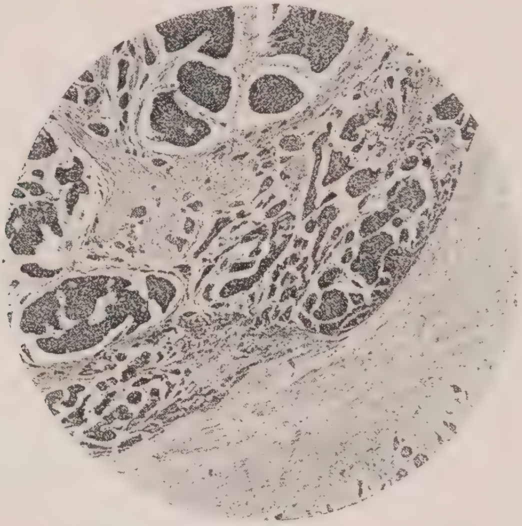

FIG. 366.—Carcinoid Tumour of Appendix, showing clumps of small polygonal epithelial cells in alveolar spaces. × 30.

Sarcoma of the intestine is comparatively rare. Occasionally sarcoma of ordinary type is met with in the small intestine, where it may form a somewhat pedunculated growth. *Lymphosarcoma* is somewhat commoner; it is usually found in the small intestine, where it may be of very diffuse character and involve many feet of the bowel. There is a diffuse infiltration of the mucosa and submucosa with a soft cellular tissue; both coats are much thickened and raised, whilst ulceration may follow. Sometimes apparently separate foci of growth occur, especially in the Peyer’s patches. In cases of lymphosarcoma there is usually extensive involvement and enlargement of the mesenteric lymphatic glands; and the whole condition may be called intestinal *lymphosarcomatosis*.

Secondary growths of the intestine, apart from invasion by way of the peritoneum, are extremely uncommon though melanotic tumours are occasionally met with. The peritoneum is frequently the seat of secondary carcinoma (p. 586) and the bowel may become invaded from the serous surface and its lumen considerably contracted.

Congenital Abnormalities. The commonest of these is the occurrence of a Meckel's diverticulum, which represents the proximal end of the omphalomesenteric duct. The diverticulum, is of elongated form, measuring up to about six inches in length, and is somewhat narrower than the small intestine. Occasionally it is adherent at the umbilicus and in some cases a fistula is present ; or again, there may be obstruction at the proximal end, sometimes merely by a fold, and accumulation of mucus occurs so that an *entero-cyst* results. A Meckel's diverticulum rarely leads to any serious results, but when it is adherent it may cause volvulus of the small intestine or even more severe strangulation. It may be added, that in the adult the diverticulum occurs usually between three and four feet above the ileo-cæcal valve ; and at about half that distance in young children. Carcinoma has occasionally been observed to develop in the apex of a Meckel's diverticulum.

Stenosis or actual *atresia* may occasionally occur in the intestines. In the small intestine, the commonest site is at the orifice of the common bile-duct or at the ileo-cæcal valve. Occasionally a part of the intestine is completely absent, a condition which is usually associated with evidences of other malformations. The commonest site of atresia, however, is at the lower end of the rectum, and this may occur in varying degree. Sometimes a dimple in the skin, representing the anus, is separated from the lower end of the rectum by a thin layer of tissue —the condition being known as *imperforate anus*. In other cases, however, the lower end of the rectum may be absent for some distance—*atresia recti*. In association with the latter condition, there may also be a fistulous opening between the lower end of the bowel and the bladder or urethra in the male; in the female the communication is with the vagina.

THE PERITONEUM

Acute Peritonitis. Infection of the peritoneum by organisms takes place in a great variety of ways and the effects are of all degrees of severity. The resulting lesion may be a relatively slight inflammation in a restricted area, the exudate afterwards becoming absorbed or undergoing organisation ; in the latter case fibrous adhesions result. On the other hand, virulent organisms may rapidly invade the peritoneal sac widely, and lead to a fatal result, even when inflammatory changes are at an early stage. At a post-mortem examination in such a case, the intestines are usually in a state of paralytic distension and contain much fluid material and gas. The bacterial toxins apparently act on the muscle directly and lead to the dilatation, whilst absorption by the bowel is interfered with, and at the same time there is probably increased secretion ; thus the accumulation of fluid results. The surface of the bowel is intensely congested, small hæmorrhages are present, the serosa is dull, and there are flakes and strands of lymph between the coils, gluing them together ; also a certain amount of fluid exudate may be present at places, especially posteriorly and in the pelvic cavity. Such is the usual picture in a case of acute general peritonitis, but the amount and characters of exudate vary greatly. Sometimes there is merely a blood-stained and somewhat turbid fluid, in which there are swarms of bacteria; such a condition may be met with in streptococcus and in mixed infections. The profound toxæmia and rapidly fatal collapse can be readily understood, seeing that, on the one hand, the area of bacterial multiplication is so extensive and, on the other hand, absorption takes place so rapidly from the peritoneal cavity both by blood vessels and by the lymphatics of the diaphragm. In some cases the organisms likewise become absorbed and a septicæmic condition is present. Whilst the general effects in peritonitis are chiefly the result of toxic absorption, symptoms are also due to the paralytic ileus which occurs in varying degree.

In acute peritonitis there are evidences of marked toxic action in the various organs throughout the body—cloudy swelling and early fatty changes, and in the liver not infrequently areas of necrosis.

Varieties. The varieties of peritonitis, described according to the characters of the exudate as *serous*, *fibrinous*, *hæmorrhagic*, *fibrino-purulent*, and *suppurative*, correspond with those seen in other serous sacs, and accordingly do not need to be described in detail. There is, however, a special form in the case of the peritoneum, namely, that which is the result of perforation, and in which some of the gastric or intestinal contents escape into the cavity. In such cases a varying amount of the escaped material is found mixed with exudate, usually of a serous and hæmorrhagic character; and numerous bacteria of great variety are present. Perforation is usually attended with symptoms of shock, etc.

One point of importance in connection with the peritoneum as compared with other sacs is that, owing to the complicated arrangement of the serous membrane, the inflammatory process may remain localised or it may become generalised, and the resulting effects are very different in the two cases, as will be illustrated below. It is to be noted that the peritoneum, in virtue of the cells which pass into it, has great powers of resisting bacterial invasion. On the other hand, once bacteria have gained a foothold there is the possibility of their spreading and infecting a large surface. The spread is often prevented by plastic adhesions, aided by immobility of the abdominal wall and a varying degree of local paralysis of the intestine.

Conditions of Occurrence. Some of these have already been noted in connection with lesions of the stomach and bowel, and others will be referred to later, especially in relation to diseases of the female genital tract. The causes are very numerous and we shall give only a survey of the main groups. The sources of infection may be conveniently arranged from the practical point of view in three main groups, viz. (*a*) lesions of the alimentary tract, (*b*) lesions of the pelvic organs, and (*c*) lesions of the solid viscera, retro-peritoneal tissue, etc.

(*a*) In the majority of cases of acute peritonitis, the bacteria reach the peritoneum from a lesion of a hollow viscus, usually the stomach or the bowel, but occasionally the gall-bladder. This occurs in connection with such conditions as gastric ulcer, typhoid, dysentery, ulcerated new growths, fæcal ulcers (p. 579), whilst acute appendicitis is the commonest cause of all. Accordingly, in investigating any case of peritonitis *post mortem*, all these parts must be carefully examined. Then there is the whole group of cases where there is some mechanical interference with the bowel, e.g. strangulated hernia, intussusception, etc., as has already been described. Peritonitis may occur secondarily also in infarction of the small intestine, due to plugging of the superior mesenteric artery. If these lesions are considered as a whole, it is to be noted that in some cases there is actual *perforation*, whilst in others the bacteria reach the peritoneum by spread through the wall at the site of the lesion. Acute peritonitis in connection with an inflamed gall-bladder, for example, occurs in both these ways, lymphatic extension with localised peritonitis being the more common. But occasionally rupture of a necrotic portion of the wall takes place and the contents escape; a fatal general peritonitis then usually results. A similar statement applies to the bladder when it is the seat of septic cystitis.

(*b*) In the case of extension from the pelvic organs peritonitis arises, as has been said, most frequently in infections of the female genital tract. Here there are two chief modes of spread, namely, (1) by direct extension from the serous covering of a viscus, and (2) by way of the Fallopian tubes. It may be noted that although in most cases the mode of extension of the inflammatory process can be traced, this sometimes may not be possible. Peritonitis often occurs secondarily to gonorrhœal salpingitis; it is usually a local acute condition which often leads to adhesions, but occasionally localised suppuration may follow. Various other inflammatory conditions of the uterus and tubes may lead to peritonitis, the most important being those of puerperal nature, which are often caused by streptococci and are sometimes of a rapidly fatal character. Peritonitis due to pneumococcus is not infrequently met with in children. It has been recognised that it is more common in the female sex, and Macartney has shown that the infection takes place by way of the genital tract. In most cases the pneumococci belong to types I and II (p. 394). Again, peritonitis, either localised or general, may arise in connection with septic cystitis, this occurrence being commoner in the male sex.

(*c*) Peritonitis due to infection from solid viscera is less common, but there are a considerable number of lesions which may give rise to it. As examples, we may mention suppuration in the liver, hæmorrhagic pancreatitis, septic infarction of the spleen, a ruptured mesenteric gland in typhoid fever, extra-peritoneal suppuration, etc. As a rule, in such cases the origin of the infection can be readily traced.

Hæmatogenous infection of the peritoneum also occurs, but is much rarer than in the case of other serous sacs. It is met with occasionally in Bright's disease, septicæmia and infective fevers, but the possibility of local spread of the organisms must always be considered.

The bacteria met with in peritonitis vary greatly according to the conditions and mode of spread, as will be readily understood. Thus any organisms of the pyogenic group may be concerned, also the typhoid bacillus, gonococcus, proteus bacilli, and various anærobes. We may say, however, that when infection originates from the alimentary tract without perforation, bacilli of the coli group and streptococci are those most frequently concerned ; and many of the most acute cases are due to the latter, though the virulence varies greatly. The effects of B. coli are usually less severe, and a diffuse suppurative peritonitis due to this organism may exist for some time before a fatal result is produced.

Chronic peritonitis, which is usually localised in distribution, may occur secondarily to an acute attack, as just described, or may be of chronic nature from the beginning. The latter condition is met with as a result of any chronic lesion in a viscus—for example, chronic gastric ulcer, chronic cholecystitis, gumma of liver, and sometimes in association with cirrhosis of the liver, etc. It is common also as a secondary result of cancerous growths and is a well-marked feature in tuberculosis of the peritoneum, as will presently be described.

Chronic Hyperplastic Peritonitis. This is a comparatively rare but interesting condition in which, along with adhesions between the viscera, there occurs great hyaline thickening, especially of the visceral peritoneum. The distribution of the lesion varies considerably, but the liver is often specially affected and may be covered by glancing laminated connective tissue of whitish appearance, which at places may reach half an inch in thickness or even more. The term ' sugar-iced liver ' (Zuckergussleber) has been applied. The thickening may be attended with a certain amount of subcapsular fibrosis and occasionally there is a certain degree of cirrhosis throughout the substance. A similar change may occur on the surface of the spleen and there is often fibrous thickening with retraction of the omentum and mesentery. The chief effect is an intractable ascites requiring repeated tappings. Such a condition is often associated with similar changes in the pericardium, pleuræ and mediastinal tissues, and great thickening of the serous membranes, especially of the lower parts of the pleuræ, may be present ; we may thus speak of a *polyserositis.* (Other names have been applied, e.g. *Concato's disease* when all the serous sacs are involved, *Pick's disease* when the pericardium and peritoneum over the liver are implicated ; but these seem to be merely varieties of the same condition.) Microscopic examination of the thickened areas shows merely laminated hyaline connective tissue in a relatively avascular state. With regard to the etiology, it is not possible to say anything definite. Rheumatism has been supposed to play a part in some cases, granular kidneys have been present in others ; but no explanation of the remarkable hyaline thickening can be offered.

Tuberculosis of the Peritoneum. The peritoneum is often the seat of tuberculous infection, and this may be conveniently described as of two main types, namely, a *general* and a *localised.* The origin of the generalised type may be a caseous lymphatic gland, as is not uncommon in tabes mesenterica, or the bacilli may reach the peritoneum from a tuberculous Fallopian tube, either directly through its covering or by way of its abdominal opening. In other cases where no gross lesion can be found, the infection is probably by the blood stream, a small focus forming from which dissemination afterwards occurs. The condition of the peritoneum varies widely in different cases. There may be an eruption of very minute grey tubercles all over the peritoneum, which may or may not be attended by inflammatory change. The omentum is often extensively involved and forms a large mass across the upper part of the abdomen. Then again, the infection may be accompanied by caseous change, which may take place in foci here and there, or may be in the form of a more diffuse caseous suppuration. Lastly, one meets with cases where the tubercles are comparatively scanty and where the chief result is formation of adhesions, which may be attended by serous effusion between them. When chronic tuberculous peritonitis is associated with ulcers of the intestine, ulceration may occur between the adjacent loops of the bowel.

Ascites. Serous effusion into the peritoneum, of a purely dropsical character, is met with in cases of general œdema both of the cardiac and renal types, and is sometimes of marked degree ; a certain amount of accumulation of fluid may occur also in severe anæmias and wasting diseases. The most marked examples of ascites, however, are the result of portal obstruction, and the accumulation of fluid is often very great and leads to enormous distension of the abdomen. The commonest cause is atrophic cirrhosis of the liver, but the ascites may result from conditions outside the liver, which lead to pressure on the portal vein, such as tumour growth, chronic inflammation with contraction, etc. In the conditions mentioned the ascites is purely dropsical in nature and there is no formation of fibrin in the peritoneum, but in cases of portal origin it is not uncommon for a mild infection to become superadded. Then again, ascites may result from some lesion of the peritoneum—for example, disseminated malignant growth or tubercle; in such cases inflammatory reaction of varying degree is usually present and the fluid which accumulates has partly the characters of an exudate, though the protein content is relatively small. Polymorpho-nuclear leucocytes, which are absent in the purely dropsical types, are then to be found, and not infrequently there is admixture of blood in the fluid.

Tumours. Primary growths in connection with the peritoneum are of rare occurrence, and in most cases they take origin, not from the serous layer but from some adjacent structure. Thus, to mention examples, *lipoma* may arise in connection with the *appendices epiploicæ*; *fibroma* takes origin from the connective tissue and sometimes from the sheaths of the nerves in *neurofibromatosis* ; and *lymphangioma* is occasionally met with in connection with the lymphatics of the mesentery. The so-called endothelioma of the peritoneum presents characters corresponding with those of the endothelioma of the pleura, but is less frequent. Although microscopically it usually corresponds with an endothelioma, there have been cases where the cells were more cylindrical in form and of epithelial type.

Secondary growths of the peritoneum are comparatively frequent, especially in cases of gastric and ovarian carcinoma. They may be extremely numerous and of very minute size, often attended by hæmorrhage and inflammatory reaction; or there may be larger nodules and diffuse infiltration. The omentum is very frequently involved and becomes drawn together into a hard irregular mass. In some cases of cancer the chief lesion is a very diffuse infiltration with thickening of the serous layers, but with little nodular formation; by such a process the mesentery may become greatly thickened and shrunken. Such a type of lesion is often attended by marked ascites. In cases of mucoid (colloid) carcinoma the peritoneum is sometimes the seat of enormous masses of soft and somewhat translucent growth (Fig. 367). Metastases of melanotic growths are not infrequent and the peritoneum may be studded with enormous numbers of small black nodules; these tend to be specially numerous in the omentum and mesentery.

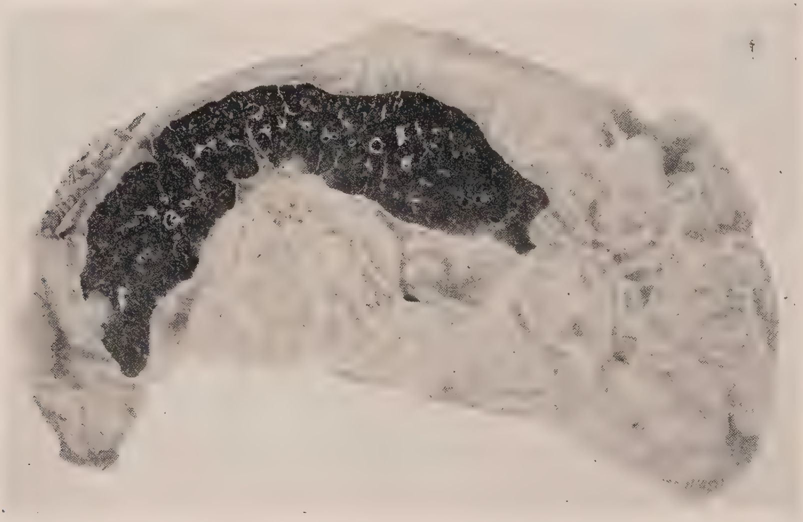

FIG. 367.—Section of Spleen embedded in large mass of Mucoid (Colloid) Cancer.

CHAPTER XIV

ALIMENTARY SYSTEM (*continued*)

LIVER AND GALL-BLADDER—PANCREAS

THE LIVER [1]

Whilst the anatomical changes in the liver in disease have been worked out pretty fully, our knowledge with regard to the associated functional disturbances is still very deficient. This is partly because the secretion of the liver cannot be obtained in a pure form, and partly because the formation of bile represents only a portion of the function of the organ, which is mainly concerned in internal metabolism. And, as a matter of fact, up till recently, the occurrence of jaundice and obstruction of the portal circulation, alterations in the size of the organ, and certain badly defined symptoms, formed the chief evidence of hepatic derangement. In recent years, the introduction of new methods for judging of hepatic sufficiency and for estimating the bilirubin and other constituents of the bile in the blood, have added materially to our knowledge, and there is hope that the pathology of liver disease will soon be in a much more satisfactory state. Our knowledge is still very deficient also as regards the etiology of certain conditions, for example, acute yellow atrophy and the cirrhotic lesions. Like the kidneys, the liver is markedly susceptible to toxic action, and, whilst the resulting structural changes can readily be studied, the nature of the poisons causing them is in many instances unknown. In connection with the minute histology, it is to be recognised that in no organ does autolytic change occur with greater rapidity than in the liver, and this fact must be kept in view in interpreting structural alterations, as appearances of damage may thus be exaggerated.

CIRCULATORY DISTURBANCES

Chronic Venous Congestion. In all cases of general venous congestion lasting for some time, due to cardiac or pulmonary disease, the liver shows characteristic changes. The intra-lobular veins and the adjacent capillaries become distended and widened, whilst the liver cells between the latter undergo atrophy and disappear. Thus the central parts of the lobules come to have a dark red colour, and contrast markedly with the peripheral portions, which have a yellowish colour owing to the fatty changes which accompany the congestion. A characteristic mottled marking is thus produced, and the term *nutmeg liver* is in consequence often applied (Fig. 4). There is often also some bile-staining of the liver tissue, and slight general jaundice is sometimes present. The nutmeg liver is usually increased in size, and firmer than the normal, and the surface in long-standing cases may be slightly granular or irregular owing to the atrophic changes in parts. Sometimes the surviving peripheral tissue undergoes compensatory hyperplasia, and, as this is greater in certain places, the marking becomes still more irregular, as is well seen in Fig. 368. This compensatory hypertrophy is met with especially in cases where the chronic congestion has started in early life. *Microscopic examination* shows that there occurs a gradual widening of the hepatic capillaries around the dilated intralobular veins at the expense of the liver cells, which at certain stages may be seen to be atrophied and to contain granules of pigment. This change goes on until the columns of liver cells have quite disappeared, and the central parts of the lobules are constituted by dilated capillaries with delicate stroma between. The walls of the central veins and related capillaries undergo thickening, and there may be some general thickening of the portal connective tissue; in this way, the liver tissue becomes somewhat increased in consistence. The accompanying nutritional disturbances probably play the chief part in the atrophy and disappearance of the liver cells. Actual necrosis of the surviving liver cells most centrally placed and hæmorrhage into the trabeculæ may sometimes be observed in post-mortem specimens, but these changes probably occur shortly

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[1] For full details, see *Diseases of the Liver, etc.*, by H. D. Rolleston and J. W. McNee, 2nd edition, London, 1928.

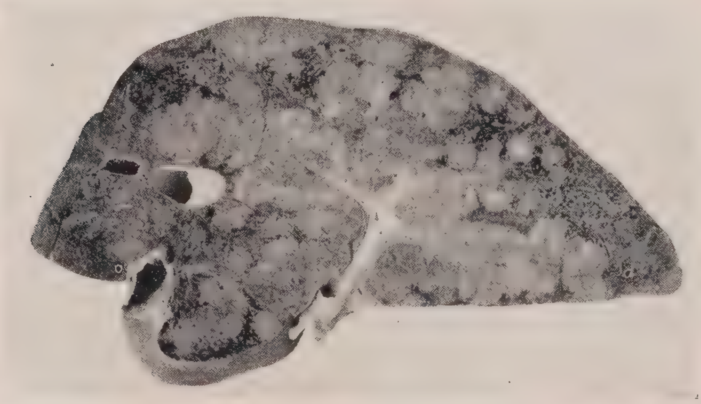

Fig. 368.—Section of Liver in long-standing chronic Venous Congestion, showing hypertrophic areas of pale appearance. × $\frac{2}{3}$.

before death, and it is not clear that they play a part in the development of the ordinary structural changes in the nutmeg liver. The yellowish colour at the periphery of the lobules is due to fatty changes. Occasionally, but rarely, true cirrhosis may be present, which is distinctly central in distribution.

Vascular Obstruction. Obstruction of the *portal vein*, which may be due to thrombosis or tumour growth, does not produce any serious effect on the structure of the liver. There is said to be at first a diminution in the amount of bile formed, but later the function of the organ appears to be well maintained. Thrombosis may be due to disease of the wall of the vein—chronic phlebitis or phlebosclerosis—which is often of syphilitic origin ; it is sometimes seen in cirrhosis of the liver and may result from spreading thrombosis from a branch, e.g. the splenic vein. It may result also from compression from without or invasion of the wall by a tumour, and it has sometimes been observed to occur after injury. The effect is a marked passive hyperæmia of the portal system, with great enlargement of the spleen, and ascites may follow. In two cases of chronic portal obstruction which we have observed, there was an abundant formation of new vascular channels in the portal fissure, so that a cavernous type of tissue had formed. The effects of suppurative thrombosis are described below (p. 609). Closure of a branch of the portal vein may sometimes be followed by a red infarction, especially when there is venous congestion or imperfect cardiac action. Such infarctions are, however, not hæmorrhagic, but, as already explained, are due to an engorgement by blood from the adjacent vessels, with consequent atrophy of the liver cells (p. 27). It has been found that in the rabbit, ligature of a branch of the portal vein leads to a simple atrophy of the area supplied, the latter undergoing great shrinking. If, however, the animal is weak, widening of the capillaries may occur, as is usually met with in the human subject (Rous and Larrimore).

Obstruction of the *hepatic vein*, which is very rare, or of its branches (the latter not infrequently produced by tumour growth), is followed by an intense engorgement of the liver tissue and a certain degree of atrophy of the liver trabeculæ.

Closure of the trunk of the *hepatic artery*, as has been shown by experimental ligature, produces anæmic necrosis of the liver—no doubt by cutting off the oxygen supply. Obstruction of its branches, however, owing to the collateral anastomosis, is usually without effect, but sometimes small areas of anæmic necrosis may form from blocking of the smallest terminal twigs. This is especially likely to happen in conditions of deficient circulation, and may play a part in producing necrosis in puerperal eclampsia (p. 666).

Traumatic Infarctions. The liver is very apt to undergo rupture and multiple laceration in cases of injury—crushing, severe contusion and the like—and hæmorrhage from it into the peritoneum may lead to a fatal result.

Portions of the liver tissue may have their blood supply cut off by lacerations of the vessels, and in cases where the patient survives, these portions may undergo anæmic necrosis and assume a dull yellow colour—the term traumatic infarction is then often applied. According to our experience, the necrosis is rather of the coagulative type, and autolytic softening is not marked. At a later period healing occurs, and vascular connective tissue, in which new bile ducts may be present, forms around the necrosed tissue (p. 118).

The areas of necrotic tissue or 'infarctions,' which are sometimes met with in cases of puerperal eclampsia (p. 595) are in chief part due to the coagulation which occurs within the blood vessels as the result of toxic action, although, no doubt, direct toxic action on the liver cells themselves also plays a part.

Atrophy and Hypertrophy

The chief cause of general *atrophy* of the liver is inanition, and in this condition the liver undergoes marked diminution in size. The lobules are shrunken, and the organ often has a uniform brownish colour if no other lesion is present. A certain amount of atrophy occurs merely as a senile condition. In atrophied livers the cells, especially in the central parts of the lobules, often contain granules of brownish yellow pigment of lipoidal nature—the so-called fuscous degeneration (p. 168). Atrophy is met with also as a result of pressure, in such conditions as tumours of the liver, hydatids, etc.; another example is the wasting of the liver tissue in amyloid disease. Pressure atrophy is seen when the liver is compressed or altered in configuration over a long period of time, and may be caused by tight lacing, and by occupations which involve much stooping. In such conditions the liver is altered in shape, and antero-posterior grooves, due to lateral pressure, form on its upper surface. A shallow depressed area, over which the peritoneum is thickened and opaque, is often present anteriorly and is due to pressure of the costal margin on the surface of the liver in the act of stooping. The condition known as acute yellow atrophy is not really of atrophic nature (p. 596).

True *hypertrophy* of the liver, compensatory in nature, is of common occurrence. As already stated (p. 121), it takes place when part of the liver is experimentally removed, and in a corresponding way in many chronic lesions which lead to destruction of a part or parts of the organ. Thus it is a prominent feature in cirrhosis, in subacute yellow atrophy, in hydatid disease, and sometimes it is well marked in chronic venous congestion where there has been much loss of liver tissue (p. 588). In all such conditions, the surviving liver cells first undergo general enlargement and then division by mitosis, and in this way the liver parenchyma is increased. The hypertrophic change often occurs in foci, and the surrounding liver cells may be seen to be stretched and even somewhat atrophied. Experimental work has shown that, when as much as two-thirds of the liver has been removed, the weight of the organ may be almost regained within a few weeks. In fact, the restoration occurs so readily that endeavours to study diminished hepatic function by this method have yielded little result. The restoration of liver tissue occurs by means of hyperplasia of the surviving lobules. The term 'regeneration' which is often used in connection with the compensatory process, is thus rather misleading.

DEGENERATIONS AND NECROSIS

The liver cells are undoubtedly very susceptible to the action of poisons of various kinds. These poisons are most frequently of the nature of bacterial toxins in infections, though injurious effects are produced also by chemical substances of known nature, which may be introduced into the body by the alimentary tract, e.g. phosphorus; by inhalation, e.g. chloroform and tetrachlorethane; or even by the skin, as has been shown to occur in the case of trinitrotoluol. And the liver occupies a special position in being the organ first exposed to the action of bacteria and poisons absorbed by the portal blood. It acts as a defensive organ with regard to these and often suffers in consequence. We accordingly find that lesions of a degenerative or retrogressive nature are common, and while return to normal may follow, permanent damage may be the result in many instances. The lesions are chiefly of the nature of (*a*) *cloudy swelling*, (*b*) *fatty change*, (*c*) *necrosis*, which varies in distribution and extent, and which is often accompanied by capillary thrombosis, exudation, hæmorrhage, and leucocytic infiltration, so as to lead to what may be called acute hepatitis. Such lesions may occur together in various combinations.

Cloudy Swelling. This is a result of acute infections—specific fevers, septicæmia, pneumonia, etc. It is often accompanied by a certain amount of fatty degeneration. The liver is somewhat enlarged and of rather soft consistence; accordingly the liver substance tends to bulge slightly when an incision is made. The liver tissue is pale and somewhat pinkish and has the so-called 'parboiled' appearance. The microscopic changes have already been described (p. 140). The nuclei of the liver cells may show early necrotic change, or patches of necrosed liver tissue may be present. Whilst such changes are undoubtedly initiated by toxic action, it must be recognised that the appearances may be largely accentuated by post-mortem autolysis, which is specially active in the case of the liver.

Fatty Changes. As already explained (p. 142) we use the terms fatty infiltration and fatty degeneration as meaning an accumulation of fat in healthy and in damaged cells respectively. Both are of common occurrence together in the liver and often cannot be distinguished from one another.

Fatty degeneration is found chiefly in acute infections, in certain poisonings, and in anæmias. It is a common sequel to cloudy swelling in such conditions as septicæmia, bacterial endocarditis, peritonitis, etc., and may be associated with areas of necrosis. Here also the liver is soft and its tissue is yellowish, according to the degree of the change, but the weight of the organ usually shows little or no increase. In acute phosphorus poisoning the most extreme degree of fatty degeneration is met with, and the liver may have an almost uniform yellow appearance. In fatty degeneration generally, the fat is in the form of minute globules, like an emulsion in the cell protoplasm, but in phosphorus poisoning globules of large size are present, owing to there being much infiltration of fat from outside. Fatty degeneration is produced by chloroform, whether given by inhalation or by subcutaneous injection, and is a marked change in what is known as 'late chloroform poisoning.' This is a condition which occasionally occurs after anæsthesia, especially in young subjects. The symptoms usually appear about a day afterwards, and include vomiting often attended by hæmorrhage, slight jaundice, acidosis and collapse. In fatal cases there is marked fatty degeneration in heart, kidneys, and liver, often accompanied in the last by a certain amount of necrosis. The condition apparently represents the result of an idiosyncrasy with special susceptibility to the drug; certainly it occurs quite apart from a septic condition. The fatty degeneration in pernicious anæmia, leukæmia, etc., is mainly central in distribution, apparently affecting the parts farthest from the arterial blood supply.

Fatty infiltration occurs in varying degree in conditions of obesity and may be regarded as an exaggeration of the normal process of fat storage. It commences round the portal tracts and at an early stage these are outlined by yellow zones. What may be regarded as an extreme example is not uncommon in chronic alcoholism. The lobules may be infiltrated throughout, and the organ is increased in size, often weighing five pounds or over. Its consistence is soft and it pits on pressure, while the cut surface has an almost uniform yellow colour and a greasy appearance. In such an extreme condition microscopic examination may show each cell to be distended with a large globule of fat, the nucleus being pushed to one side; the capillaries are pressed on and obscured, so that the appearance in parts somewhat resembles adipose tissue. A somewhat similar condition is sometimes met with also in cases of chronic tuberculosis, especially pulmonary phthisis, and the condition of the liver forms a contrast to the general condition of emaciation. As shown by Dible, the amount of fat in the liver depends largely on the condition of nutrition before death. In states of inanition increase of fat occurs as the result of transference from the fat depots, apparently along with failure to utilise it.

In both fatty infiltration and degeneration resolution of the lesion may follow, and the affected cells may return to normal. It is to be noted that the fatty changes, though often associated with jaundice, may occur without its presence—they do not in themselves produce jaundice.

Pigmentary Changes. As these have been described in other chapters, only a summary need here be given. The following are the chief varieties of pigments met with in the liver :—

(A) *Atrophic Pigment.* This occurs in the form of yellow-brown granules which do not give an iron reaction and are apparently of lipoidal nature (p. 168). It is met with when the liver cells are undergoing atrophy, especially in the later years of life.

(B) *Bile Pigment.* This is present in cases of jaundice where there is obstruction to the outflow of bile. It occurs within the liver cells in the form of greenish-brown granules, especially in the central parts of the lobules, and also within the bile capillaries in the form of irregular hyaline cylinders or casts of olive-green colour. From these casts branches may sometimes be seen passing into the substance of the liver cells. They are composed of inspissated bile, probably in combination with some albuminoid material, and are sometimes spoken of as *biliary thrombi.*

(C) *Hæmosiderin.* This pigment, which gives the iron reaction with ferrocyanide of potassium and hydrochloric acid, is met with mainly in conditions where there has been excessive blood destruction or absorption from hæmorrhages. Hæmosiderin usually appears first in the Kupffer cells and may become abundant. It is found also in the form of brownish-yellow granules within the liver cells, especially at the periphery of the lobules, but in an early stage the cells may give only a diffuse iron reaction. The presence of this pigment is a prominent feature in pernicious anæmia, but it may occur in leukæmia, in malignant malaria, and in various septic conditions attended by blood destruction. The most abundant deposits of hæmosiderin are, however, met with in association with cirrhosis in hæmochromatosis (p. 166). The pigment may be in enormous quantities, not only in the liver cells, but in the walls of capillaries and in the connective tissue generally. In the normal liver the amount of iron is about 0·08 per cent. of the dried substance ; in pernicious anæmia the amount is not infrequently over 0·3 per cent., whilst in hæmochromatosis it may reach the high figure of 5 per cent. or even more. It may be noted that in the early months of life the liver normally gives a hæmosiderin reaction and this becomes more marked in wasting conditions.

(D) *Malarial Pigment.* This occurs especially in chronic cases of malarial fever and may be in such quantity as to give a dusky appearance to the liver. The pigment is in the form of very minute dark brown granules, which do not give the iron reaction, and is deposited chiefly in histiocytes in the connective tissue of the portal tracts and in the capillary walls.

Amyloid Disease. In this condition the liver increases in size and becomes firmer and elastic in consistence, and the enlarged organ with its rounded margin can not infrequently be palpated during life. The structural changes and causation have already been dealt with (p. 151). Amyloid disease does not produce jaundice, nor, as a rule, any ascites ; but the occurrence of the latter in general œdema due to the accompanying amyloid disease of the kidney, may possibly be aided by the changes in the liver.

Necrosis. Necrotic lesions are of common occurrence in infections and poisonings. The necrosed tissue has a dull yellowish colour, but the areas are often too small to allow the condition to be recognised by the naked eye ; and again, the necrosis may be attended by hæmorrhage, which necessarily obscures its presence, the lesion then appearing as a hæmorrhagic one. Minute areas of necrosis occur in various acute fevers—smallpox, scarlet fever, yellow fever, diphtheria, etc., and in various inflammatory and septicæmic conditions. The extreme example of necrosis is seen in the condition known as acute yellow atrophy, which is described below (p. 596). In some cases small areas of liver tissue are irregularly affected—*focal necrosis*; in others, a particular part of the lobules is involved—*zonal necrosis*; and the latter may be in the central, intermediate, or peripheral zones. Such a distribution manifestly depends in some way on the vascular arrangements, but it is not possible to explain the differences. One would expect that a peripheral necrosis caused by toxins carried by the portal blood, would be the commonest lesion, but this is not the case. Central necrosis is most frequently met with, and it is not uncommon in streptococcal and pneumococcal infections. It is seen in chloroform poisoning, and can be readily produced experimentally by inhalation of the drug in excessive quantities. Midzonal necrosis, though less common than the central form, is a definite and striking lesion; we have met with it in some cases of acute peritonitis, and it is described as occurring in yellow fever also. The cells in the intermediate zone throughout the liver may be seen to be of hyaline or granular appearance, without nuclei, and showing various stages of absorption (Fig. 369); whilst mitoses, indicating a process of repair, may be present in large numbers in the adjacent liver cells. Minor degrees of necrosis are sometimes found around the portal tracts in cases of acute gastro-enteritis in children, attended with round-cell infiltration (Blacklock). Such a lesion may be of importance in relation to the development of cirrhosis later in life.

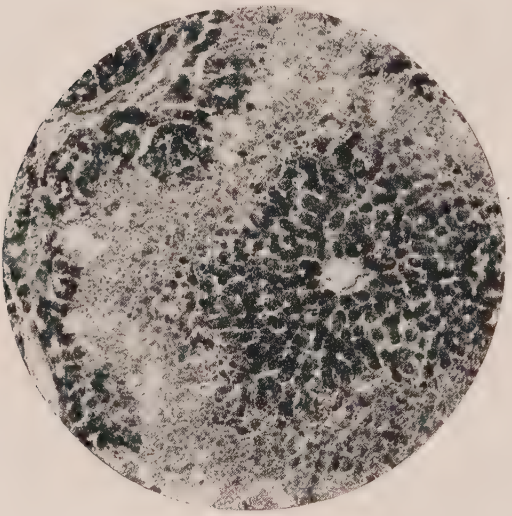

FIG. 369.—Necrosis of Mid-zonal Type.

The necrotic part, which appears pale, involves the intermediate zone, though somewhat more towards the portal tracts. (J. S. D.)

In *acute phosphorus poisoning*, the outstanding lesion is the intense fatty change already described, but there may also be necrosis of cells; and in cases where death occurs after about a week, this may be a marked feature. It appears especially at the periphery of the lobules, and as the dead cells undergo absorption, there occurs an ingrowth of bile-duct epithelium from the free ends of the minute ducts. In this way numerous new bile-ducts may be seen at the margin of the lobules, and their growth is accompanied by condensation of the connective tissue and leucocytic infiltration. As this process goes on, the liver becomes diminished in size, and the resulting condition is known as the 'atrophic phosphorus liver.' This end result is in many respects comparable with that seen in acute yellow atrophy, but there is not the widespread destruction of lobules seen in the latter condition, and the degree of fatty change is much greater.

In *puerperal eclampsia*, necrosis of liver cells is an almost invariable occurrence. In many cases the liver substance is studded with numerous small hæmorrhagic points, and these, on microscopic examination, are seen to be necrotic foci with admixture of much blood and fibrin. These foci occur especially around the portal tracts, and in cases where the patient recovers, might lead to reactive overgrowth of the connective tissue. Sometimes, however, necrosis is more extensive, and irregular yellowish areas of considerable size may be met with, attended with varying congestion and hæmorrhage. There may be in these areas necrosis of the whole liver tissue, and the condition is probably secondary to vascular damage and corresponds with the extensive infarctions which may occur in the kidneys in eclampsia (Fig. 370). The necrotic process is to be regarded as the result of a toxin acting both on liver cells and vascular endothelium, but its nature is still unknown.

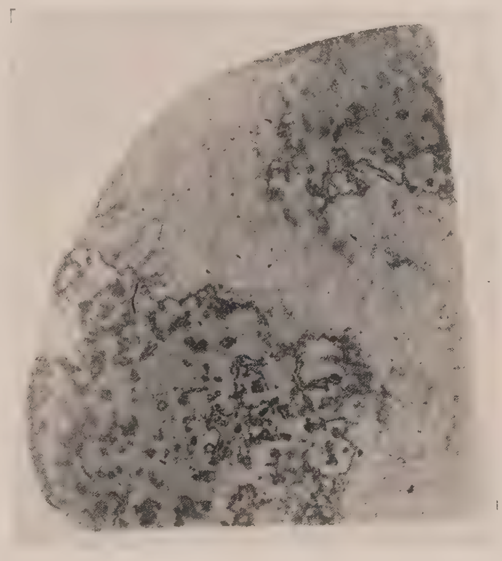

FIG. 370.—Section of Liver in Puerperal Eclampsia, showing two large areas of Necrosis and Hæmorrhage. (Natural size.)

Results of Necrosis. Necrosis of liver cells is usually followed by their absorption, provided that the capillaries have not been damaged, while the adjacent surviving liver cells multiply by mitosis and in the case of small lesions repair the columns. It has been shown by Whipple and Nurwitz that the central necrosis produced in dogs by chloroform inhalation, may be followed by repair and there may be a return to normal within ten days, and no doubt a similar result would follow mid-zonal necrosis. In other cases, however, where the damage is more severe and, especially where the periphery of the lobules is involved, overgrowth of connective tissue follows, and the bile-duct epithelium grows into the spaces formerly occupied by the necrosed liver cells. The reparative changes following severe damage, are seen in greatest degree in acute yellow atrophy.

Acute Yellow Atrophy. As already said, this is to be regarded as the extreme example of toxic necrosis, although in most cases the real nature of the poison is quite unknown. The disease is usually of rapid onset and is characterised by fever, marked jaundice, symptoms of profound toxæmia, etc., which usually lead to a fatal issue. In acute cases death may occur within a week but not infrequently the disease runs a subacute course of some weeks. It is much commoner in the female sex than in the male, and occurs especially in connection with pregnancy or the puerperium. It is occasionally met with in males, and in some cases a relation to infections or septic conditions can be made out ; in others, however, the origin is quite obscure. In children also, the disease occurs and runs a very acute course. In recent times a considerable number of cases have occurred in those undergoing treatment for syphilis with arsenobenzol compounds. The pathology of these cases is not clear, though it seems probable that such drugs produce severe toxic effects in specially susceptible individuals, possibly when the liver has been previously damaged by syphilis. Minor toxic action of arsenobenzol compounds is shown by the not infrequent occurrence of jaundice, usually of the latent type (p. 631). It may be added that lesions closely resembling those of acute yellow atrophy have been observed also in cases of poisoning with trinitrotoluol and with tetrachlorethane.

Structural Changes. The chief changes occurring in yellow atrophy may be said to be, in the first place, a rapid necrosis of liver cells, affecting large areas in an irregular manner, and in the second place, an autolysis and absorption of the dead cells. When the latter has occurred, only the framework remains and the lobules are chiefly constituted by capillaries filled with blood (Fig. 372). The necrosed liver tissue has a bright yellow colour owing to bile-staining and sometimes to fatty change, whilst the areas from which the liver cells have disappeared have a red colour—the so-called ‘red atrophy,’ which is thus a later stage. During the progress of the disease, the liver undergoes marked diminution in size, and at the time of death may be less than half the normal weight. It is then of somewhat soft consistence and flattens itself out on the table, whilst the capsule is wrinkled. The appearances vary according to the rapidity of the disease and the stage reached. In very acute cases which prove fatal within a few days, the liver may have an almost uniform yellow colour, and diminution of its size may not be marked. At a later stage, red atrophied areas become interspersed amongst the yellow tissue; whilst later still, a large part of the liver substance may be in a condition of red atrophy and the organ much shrunken. The irregular manner in which the necrosis and subsequent absorption of the liver cells take place, is a marked feature. The red parts have been aptly compared to splenic tissue, the lobules being greatly atrophied and indistinguishable by the naked eye.

In acute yellow atrophy the *kidneys*, in addition to being bile-stained, show marked cloudy swelling, and often a considerable amount of necrosis of the epithelium of the convoluted tubules with catarrh. These changes apparently represent a toxic effect similar to that which occurs in more marked degree in the liver. The urine contains albumen and tube-casts, urea is much diminished and amino-acids may be abundant, crystals of leucine and tyrosine sometimes separating out in crystalline form. These changes, which were observed at an early period of inquiry into the disease, are apparently the result of loss of the liver tissue by necrosis, its normal function in the deaminisation of amino-acids and formation of urea being thus interfered with; formation of amino-acids from autolysis of liver cells may also play a part. They are in striking agreement with the experimental results of Mann and his co-workers, who have shown that excision of the liver is followed by a marked increase of amino-acids in the tissues, blood and urine, accompanied by diminution of urea in these situations.

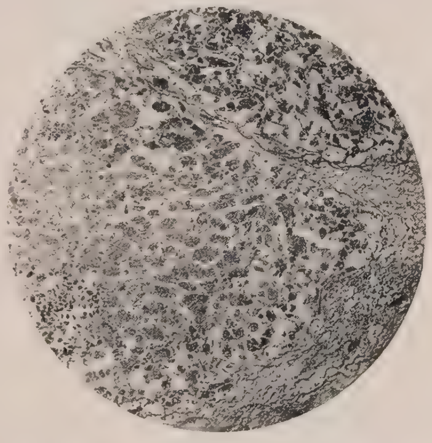

Fig. 371.—Acute Yellow Atrophy of the Liver; portion of yellow area showing general Necrosis of Liver Cells. × 60.

If a scraping from the liver be examined microscopically, necrotic liver cells, granular débris, granules of bile pigment, etc., will be found, and crystals of leucine and tyrosine may be present. On microscopic examination of sections, the affected liver cells are seen to be swollen, granular or hyaline, often somewhat angular in form, and devoid of nuclei, and the necrosis sometimes extends to the capillary walls (Fig. 371). Although fatty degeneration is sometimes present, the outstanding feature is the extensive necrosis. In the parts from which the liver cells have become absorbed, the lobules are somewhat collapsed, and consist chiefly of the hepatic capillaries filled with blood (Fig. 372). At the periphery of such lobules, even at an early stage there appears an excess of bile-ducts in the peri-portal tissue; and if life is sufficiently prolonged, these branch and make their way into the lobules, in the spaces formerly occupied by liver cells. Along with this epithelial proliferation, there occurs a proliferation of connective tissue cells around the new bile-ducts. Ultimately such lobules may be entirely replaced by cellular connective tissue, in which the bile-duct structures are more or less radially disposed. The growth of the bile-duct epithelium is, no doubt, due to the fact that when the liver cells have become absorbed, the bile-duct epithelium is left with a free extremity, and accordingly grows inwards in order to restore the continuity. Such proliferative changes may go on for weeks and even months, and the term *subacute yellow atrophy* may be applied (Fig. 373).

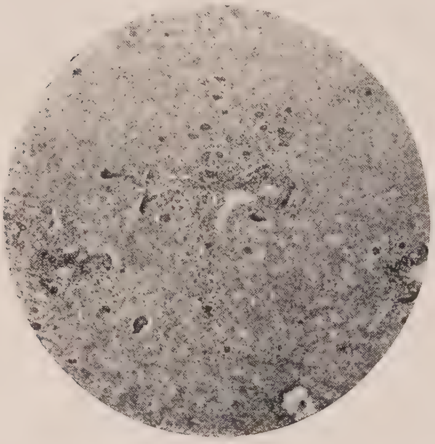

Fig. 372.—Acute Yellow Atrophy of the Liver; portion of red area, where the Liver Cells have completely disappeared and the Lobules are constituted by dilated Capillaries.

Early formation of new bile-ducts is seen around a portal tract. × 60.

The question has arisen concerning the extent to which this growth of bile-ducts leads to regeneration of liver tissue. At places one may see the cells of newly formed bile-ducts assuming the character of liver cells; but this never occurs in any marked degree, probably owing to the accompanying proliferation of connective tissue, which prevents the establishment of the normal relationship of capillaries to liver cells. Accordingly, whilst it may be that the

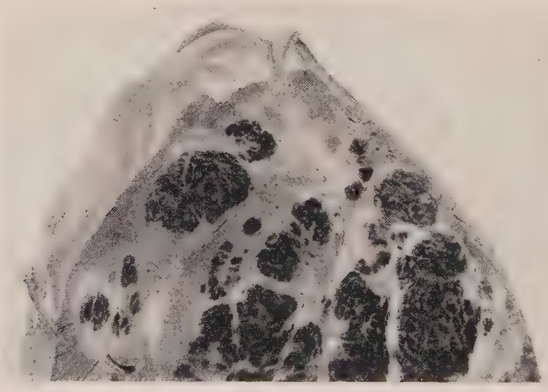

Fig. 373.—Section of Liver in late stage of Subacute Yellow Atrophy.

The dark areas represent surviving liver tissue deeply bile-stained. The pale areas are parts from which the liver cells have disappeared.

bile-duct epithelium potentially represents young liver cells, the newly formed structures at a later stage undergo atrophy rather than further development. The whole process is one of imperfect repair rather than of regeneration (Fig. 374). In some lobules where necrosis has been incomplete and most marked at their periphery, the newly formed bile-ducts may lead to restoration of continuity with the surviving liver cells. In the liver cells which escape the destructive change, mitosis may be seen, and it is chiefly by proliferation of the surviving liver cells that the liver tissue lost is, to a certain extent, compensated for.

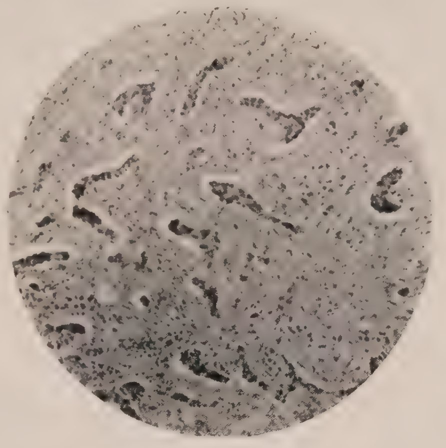

Fig. 374.—Subacute Yellow Atrophy, showing characters of newly formed Bile-ducts in young Connective Tissue. × 200.

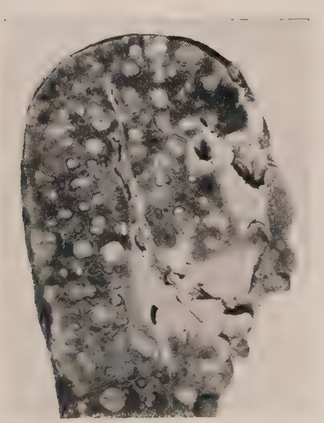

Fig. 375.—Multiple Nodular Hyperplasia of Liver.

Note the pale round nodules composed of hypertrophied liver tissue. × ⅔.

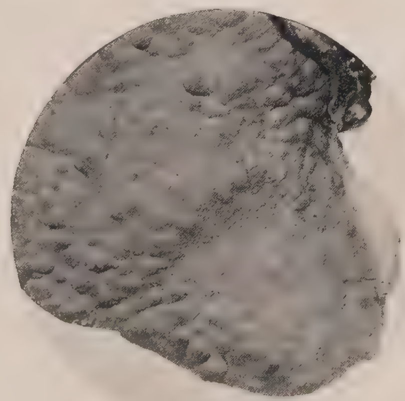

Fig. 376.—Multiple Nodular Hyperplasia.

Superficial view of same liver as is shown in Fig. 337. × ⅔.

A later stage still is met with when there has been survival of liver tissue in foci throughout the organ, and to this the term *multiple nodular hyperplasia* is suitably applied. The liver is somewhat small, and there are rounded projections on its surface (Fig. 376). On section, there is seen to be a background of fairly firm reddish tissue, against which rounded and usually yellowish areas stand out distinctly (Fig. 375). The reddish tissue is found to be vascular connective tissue, in which no liver cells are present, whilst in it there are numerous bile-duct structures which tend to have, on the whole, a radiate arrangement. The yellowish nodules are composed of hypertrophied liver tissue which has escaped destruction. Cases of this kind confirm the view that the proliferation of the bile-duct epithelium does not lead in any important degree to regeneration of liver substance. The condition is of importance as it represents, in a somewhat gross form and irregularly distributed, the lesions which occur more gradually and more generally in cases of cirrhosis. In fact, acute and subacute yellow atrophy, nodular hyperplasia, and cirrhosis, form a series of changes differing in extent and rapidity, rather than in nature; and intermediate stages are met with.

Regarding the true *etiology* of acute yellow atrophy, apart from cases where definite poisons are concerned, nothing definite is known. In the necrotic tissue one can often find groups of bacilli belonging to the coli class, but this is a phenomenon secondary to the widespread necrosis due to toxic action.

INFLAMMATORY CONDITIONS

Acute Hepatitis. In addition to infiltration of leucocytes around necrotic foci, there may be found in acute infections, especially in scarlet fever and diphtheria, infiltrations in the tissue of the portal tracts, the leucocytes being arranged in clumps or diffusely. They are usually mononuclear cells or lymphocytes. In typhoid fever a common occurrence in the liver is the presence of rounded collections of these cells, sometimes spoken of as lymphomatous nodules. They are of about the size of miliary tubercles, and are chiefly composed of mononuclear leucocytes and histiocytes which have proliferated, the liver cells becoming destroyed and also absorbed; lymphocytes are present also, especially at the periphery. A certain amount of necrotic change may be present in the centre of the nodules. We have usually failed to find typhoid bacilli within the nodules, and such is the general experience. This, however, does not exclude the possibility that they are set up by bacilli, which are afterwards destroyed. It is, however, not possible to draw a line between degenerative and necrotic lesions with leucocytic reaction, and what is often described as *parenchymatous hepatitis.*

Weil's Disease or Spirochætosis icterohæmorrhagica is an example of a disease in which the liver is invaded by the parasite *Leptospira icterohæmorrhagiæ*, yet the changes are of a somewhat ill-defined character. The chief lesion is damage to the liver cells which results in varying degrees of necrosis irregularly distributed. There is often also a distinct separation or dislocation of the liver cells. Regenerative changes may be found in the neighbourhood of the necrosed cells. Jaundice is usually a marked feature and the blood gives a biphasic van den Bergh reaction. The liver cells in the central parts of the lobules not infrequently contain bile pigment and this would point to there being an intralobular interference with the flow of blood along the bile capillaries.

A very important group of inflammatory conditions of the liver is produced by the actual presence of pyogenic organisms, and abscess formation results—*suppurative hepatitis.* We shall, however, first consider the subject of *chronic hepatitis* or *cirrhosis*, which may be the sequel to acute damage from toxins or may be of chronic nature throughout. As we have said, no hard and fast line can be drawn between cirrhosis and the reparative changes which follow extensive necrosis of liver tissue as seen in the forms of yellow atrophy (p. 596).

Cirrhosis or Chronic Hepatitis. In cirrhosis of the liver there are two essential changes, namely, (*a*) increase of connective tissue and (*b*) damage to, and loss of, liver cells. There has been discussion as to which is the primary change, but we think that neither causes the other, and that the two changes are the direct result of one factor ; that is, the liver cells become directly damaged by some toxic agent, whilst the connective tissue increases in response to irritation. The distribution of the connective tissue varies greatly, and the cirrhosis is named accordingly. In some cases several lobules are enclosed—*multilobular or coarse cirrhosis*, in others single lobules are enclosed—*monolobular or fine cirrhosis* ; whilst in others, again, the connective tissue occurs along the hepatic capillaries—*pericellular cirrhosis* ; or it may be irregular and diffuse. These varieties must, however, not be regarded as indicating distinct and separate types, as combinations and intermediate forms are met with. The terms ‘ atrophic ’ and ‘ hypertrophic cirrhosis ’ are frequently applied according as the liver is diminished or increased in size. Their use is convenient, but it must not be inferred that enlargement in a cirrhotic liver is due to hyperplastic changes in the liver cells, as it may result from the large amount of fibrocellular tissue or from an associated accumulation of fat.

The characters of the connective tissue also vary ; in some cases it may be fibrous and dense, and appear as pale grey bands in the liver substance, whilst in others there may be much formation of new blood vessels, and the tissue may be of a reddish colour. As far as the cells are concerned, the essential process may be a piecemeal destruction, the result of repeated damage over a long period. On the other hand experimental work and also the facts with regard to yellow atrophy show that cirrhosis may be the result of a single damage. In either case loss of liver substance is followed by a compensatory hypertrophy of the surviving liver cells. These undergo enlargement and may contain more than one nucleus, or a nucleus of convoluted type, and they proliferate also by mitotic division. In this way hypertrophic areas are formed and the loss of liver substance may be in part compensated for.

The destruction of cells may be more marked at one part of the lobule than at another, and accordingly a hepatic vein may be situated quite at the side, whilst the other part of the lobule has undergone great compensatory enlargement; and some lobules are completely destroyed (Fig. 377). The architecture of the lobules thus becomes greatly distorted. A common result of cirrhosis is the production of irregularity of the surface, and this is especially the case in the coarse or atrophic type.

In various kinds of cirrhosis, *newly formed bile-ducts* are commonly present in the connective tissue, and with regard to the origin of these there has been considerable dispute. It would appear, however, that they may originate in two ways. In the first place, when the liver cells at the periphery of a lobule become necrosed, absorption follows, and then the bile-duct epithelium which is thus left free grows along the space formerly occupied by liver cells, until a continuity with surviving liver cells has been established. This process is seen on a large scale in acute yellow atrophy of the liver. The second method of formation is by a change in the liver cells, when they are cut off by the growing fibrous tissue. This is probably because their relationship to the capillaries is disturbed and their function is thus interfered with. In these circumstances they lose their distinctive appearance or become de-differentiated, and come to resemble the bile-duct epithelium (Fig. 377).

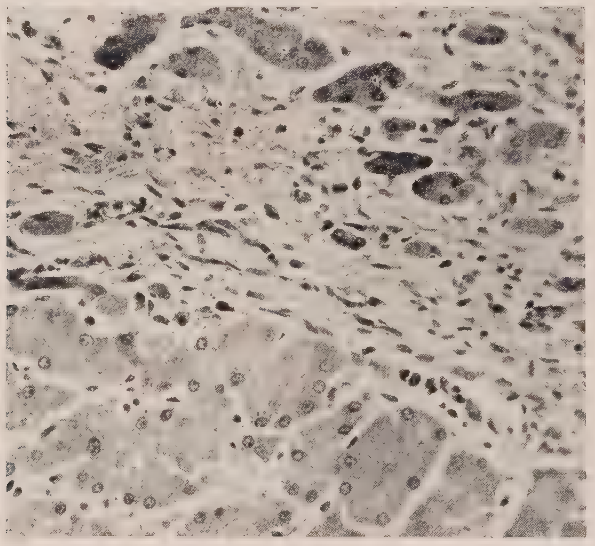

Fig. 377.—Coarse Cirrhosis of Liver. Below, a collection of hypertrophied liver cells; above, liver cells becoming atrophied and like bile-duct epithelium.

In only a relatively small proportion of cases of cirrhosis—those due to biliary obstruction, syphilis, etc.,—is the etiology understood; in the majority of instances we can only speak of poisons of unknown origin. It has been established that numerous substances which act as poisons to the liver cells, lead to cirrhosis as a result, and the anatomical changes have been minutely studied. For example, cirrhosis has been produced by manganese chloride (Findlay), by copper salts (Mallory), by tar (Davidson), by sudan III along with sodium cholate (J. S. Young), etc. The last mentioned has in a recent research found that, by varying the dosage, the lesions of acute and subacute atrophy, multiple nodular hyperplasia and cirrhosis can be produced. And a point of special interest is that each of these changes may follow the injection of a single dose. In experimentally produced cirrhosis it has been shown that much of the newly-formed connective tissue may undergo absorption at a later stage and disappear (Cameron). When, however, the condition has lasted a certain length of time the cirrhosis is permanent. One cannot say to what extent these results apply to the human subject. It is interesting to note that a considerable proportion of the substances which are most active as liver poisons, are soluble in fat, e.g. phosphorus, tar, sudan III, etc. Another fact of importance, as illustrative of the effects of toxic action, is that a definite form of cirrhosis occurs in sheep and horses as a result of eating ragwort (*Senecis jacobœa*). It is met with notably in New Zealand. Still another possibility with regard to the causation of cirrhosis has recently been opened up. It has been shown by Rich and Hamilton that in rabbits fed with a diet from which yeast has been excluded but containing sufficient B vitamins, cirrhosis of the liver develops after two or three months. It is of slowly progressing nature with little evidence of necrosis followed by reparative change. The nature of the factor has not yet been determined. It is thus seen that so far as experimental work is concerned, hepatic cirrhosis may be brought about in various ways.

In addition to the general disturbance of hepatic function which occurs in many cases of cirrhosis, two important effects may be produced, viz. interference with the portal circulation resulting in *ascites*, and interference with the excretion of bile, resulting in *jaundice*. Their occurrence varies in different types, but it may be said generally that the former is the common result of coarse atrophic cirrhosis, whilst the latter is a prominent feature of the hypertrophic or Hanot type (p. 606). It may be added that cirrhotic livers not infrequently become the seat of more extensive necrotic change, with or without the actual presence of bacteria, and thus more acute symptoms may develop before death.

Varieties of Cirrhosis. Classification of cases of cirrhosis is unsatisfactory owing to deficiency in our knowledge of the true cause in many cases. It may be made either on an etiological or on an anatomical basis, but the results do not correspond in the two cases. The same causal agent does not always produce the same results, nor is a given type of cirrhosis always produced by the same cause.

We shall describe the main *anatomical types* and discuss their etiology. If we except the syphilitic cases, which form a definite class, we may say that there are two main types—a coarse cirrhosis which is usually attended with shrinking of the organ, and a finer cirrhosis associated with enlargement. It must be recognised that intermediate forms occur, and that an enlarged cirrhotic liver may pass into the atrophic stage. One meets, however, with many cases of cirrhosis which do not conform to any particular type.

1. *Coarse Atrophic Cirrhosis of Lænnec, Multilobular Cirrhosis, or Hobnail Liver*—sometimes called 'alcoholic cirrhosis' or 'gin-drinkers' liver,' owing to its supposed common causation. The liver is reduced in size and of firm consistence, while the surface is coarsely granular or nodulated (Fig. 378); in extreme cases the weight may be less than half the normal. On section the liver substance is seen to be broken up into islets by strands of connective tissue, many of the islets being of considerable size, comprising several lobules. The liver tissue is not infrequently of a brownish-yellow tint owing to the presence of fatty change. Microscopic examination shows the changes described above (Fig. 379). The connective tissue is usually dense, and in it may be seen newly formed bile-ducts, though these are not so numerous as in the next variety. Patches of necrosed liver cells are not uncommon and hyperplasia of liver cells is well marked. The chief effect of atrophic cirrhosis is portal congestion with splenic enlargement, and this is ultimately followed by ascites, which often necessitates the withdrawal of large quantities of fluid. Thrombosis

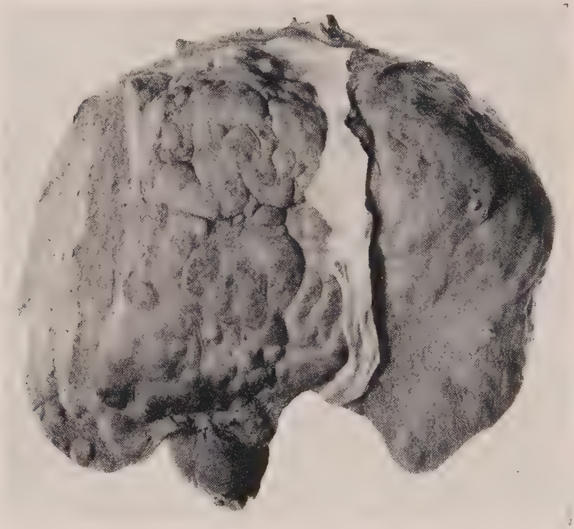

FIG. 378.—Atrophic Cirrhosis of Liver with very coarse nodularity. The organ weighed 30 oz.

of the portal vein occasionally occurs as a complication ; it intensifies the portal destruction and the ascites. Varicosity of the œsophageal veins above the cardiac orifice of the stomach develops, and hæmatemesis, sometimes fatal, may result. There is a similar condition of the lower hæmorrhoidal veins, again often with hæmorrhage (p. 22). Cases of atrophic cirrhosis often run their whole course without any visible jaundice ; slight jaundice may, however, sometimes be present and ' latent jaundice ' is not infrequent.

Atrophic cirrhosis may be produced by the taking of alcohol in excess, certain forms of spirits, gin for example, being regarded as specially apt to produce it. We consider, however, that to use the term alcoholic cirrhosis as synonymous with atrophic cirrhosis would be a great mistake. Our experience is that cirrhosis of the liver in any form is not a common lesion in chronic alcoholism. Apparently in certain places where gin-drinking is common atrophic cirrhosis is more frequently met with. In India cirrhosis of different types is comparatively common, and in most cases alcohol can be definitely excluded as an etiological factor. The commonest effect of alcohol on the liver is an extreme fatty infiltration, and this is sometimes associated with a fine cirrhosis, the weight of the organ being much increased. It has not been found possible to produce cirrhosis experimentally by means of alcohol. It has accordingly been supposed that alcohol, if concerned at all, produces chronic gastric and intestinal catarrh, and that toxins absorbed in such conditions damage the liver cells and bring about cirrhosis. Another suggestion recently made is that cirrhosis in alcoholics is due to vitamin B_1 deficiency in their food, but as to this no evidence is yet available. In a con-

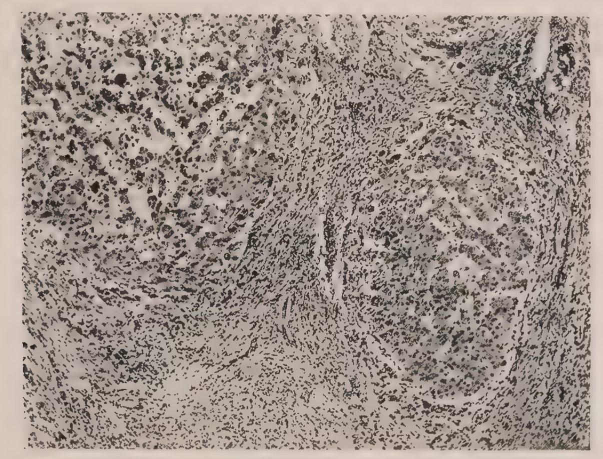

Fig. 379.—Coarse Cirrhosis of the Liver, showing broad Bands of connective Tissue between islets of Liver Tissue ; a few Bile-ducts are seen in the connective Tissue. × 45.

siderable proportion of cases of atrophic cirrhosis, however, one may say that alcohol as a cause may be definitely excluded. Such cases may occur in quite young subjects, and it seems most likely that they are the result of damage done to the liver in various infections, such as scarlet fever, etc. There is an analogy to such an occurrence in the case of the kidneys, but the sequel of changes has not been traced in the same definite way in the case of the liver. It seems to us likely that quite a fair proportion of cases of atrophic cirrhosis are post-infective in nature. As another possible cause, syphilis may be mentioned. It is generally accepted that the rarer form of congenital syphilitic cirrhosis, that in which the newly formed connective tissue occurs in definite strands (p. 611), may give rise later to a nodular or coarse cirrhosis. We do not think, however, that there is any evidence that a general cirrhosis is produced by adult syphilis. It is noteworthy that in cases of cirrhosis associated with lenticulate degeneration in comparatively young subjects, Kinnier Wilson found no evidence of syphilis or alcoholism (p. 717). In this disease a familial element is present, and it is interesting that in rare instances this is the case apart from lenticulate degeneration, several cases of cirrhosis of the liver occurring in the earlier years in members of the same family. In the syndrome, known as Banti's disease, atrophic cirrhosis occurs along with great splenic enlargement and anæmia (p. 497), but here also the etiology is unknown.

2. *Hypertrophic Cirrhosis.* In this form the liver is enlarged, sometimes weighing five pounds or more, and the surface is finely granular like morocco leather, or almost smooth. On section, the islets of enclosed liver tissue are of small size, though they do not always correspond with single lobules. Two main types of fine hypertrophic cirrhosis are usually described, namely (A) a type occurring without obstruction to the main bile-ducts, and (B) one due to such obstruction. The former was described fully by Hanot and is often named after him. There are, however, other forms of cirrhosis with enlargement. We have already mentioned the occurrence of a fine cirrhosis in alcoholism in association with marked fatty infiltration, and again, we have met with cases of marked enlargement, with jaundice, where the etiology was obscure. In some such cases there has been a history suggesting damage to the liver in connection with pregnancy. The cirrhotic liver in *hæmochromatosis* (p. 166) also nearly always shows distinct enlargement ; the condition is sometimes known as 'pigment cirrhosis.'

(A) *Hanot's Hypertrophic Cirrhosis.* In this type, as described by Hanot, marked enlargement of the liver is associated with jaundice, but there is no obstruction of the main ducts and bile is present in the stools. The structural changes are closely similar to those in obstructive biliary cirrhosis, and there are numerous newly formed bile-ducts in the periportal tissue. The jaundice results apparently from implication of these and the bile capillaries. In some cases there has been found evidence of irritation of the small bile-ducts in the form of catarrhal change, but in others this has been absent. It has been supposed too that biliary stasis resulting from increased viscosity of the bile may play a part, the liver cells at the periphery of the lobules suffering first from its effects. There is usually marked enlargement of the spleen, the organ sometimes weighing upwards of two pounds, but ascites is not produced. Death is sometimes preceded by severe toxic symptoms with hæmorrhage—the so-called *icterus gravis*. Cases conforming more or less closely to this description are occasionally met with in this country, but they appear to be more common in France. Nothing is known of their true etiology, and accordingly it is not possible to say whether such cases form a definite disease. The general distribution points to a toxic action as the cause, rather than to an actual bacterial invasion of the liver, and the close similarity of the histological changes to those resulting from gross biliary obstruction points to some irritation spreading from the bile in the bile capillaries. This type of cirrhosis is sometimes called *non-obstructive*, but this term applies merely to the large bile-ducts.

(B) *Obstructive Biliary Cirrhosis*. Experimental occlusion of the main duct in animals is followed by cirrhosis only in some instances, and the varying results seem to depend on the properties of the bile in different animals. In rabbits, ligature of the common bile-duct is followed within a comparatively short time by the occurrence of minute necroses of liver cells around the portal tracts. These form without the presence of any bacteria and are apparently the result of the direct action of the stagnant and concentrated bile on the liver cells. Thereafter, overgrowth of the connective tissue round the necroses follows and gradually extends till a general cirrhosis results. A similar condition is occasionally found in the human subject as the result of occlusion of the main bile-duct. The liver is usually of dark olive-green colour owing to the long-standing jaundice, and its surface presents a fine granularity, though sometimes this is little marked (Fig. 380). In adults, however, bacteria are usually present, and extensive necrosis with abscess formation is much more frequent than cirrhosis. In the condition of congenital obliteration of the bile-ducts a fine, practically monolobular, cirrhosis is often present. This condition, which is attended by marked jaundice, leads to the death of the child shortly after birth, and the associated cirrhosis is of interest as it develops during intra-uterine life.

In biliary cirrhosis a large number of new bile-ducts is usually a prominent feature, these having grown into the necrotic areas, as already explained (p. 598). There is no ascites or other evidence of obstruction to the portal circulation, though the spleen may be somewhat enlarged. There is, of course, intense jaundice with absence of bile in the stools, provided that there is complete obstruction.

Other Causes. Cirrhosis is sometimes stated to be produced by malarial fever, but this has been questioned. In any case, such an occurrence is not common, and it is certain that there may be great accumulation of pigment in the liver without any distinct increase of connective tissue. In *kala-azar*, however, cirrhosis occurs with moderate frequency. The organ is usually enlarged, and though there may be considerable increase of connective tissue, the surface is comparatively smooth. In the connective tissue, numerous parasites (' Leishman-Donovan bodies '), mostly in a degenerated condition, may be found. In *bilharziasis*, in certain cases the worms may be present in the portal branches in the liver, and may discharge their ova into the surrounding tissue. A somewhat characteristic cirrhosis results, there being areas of dense white connective tissue around the portal tracts (Fig. 381). In *hæmochromatosis* (p. 166) the cirrhosis is usually of somewhat fine type and is attended by en-

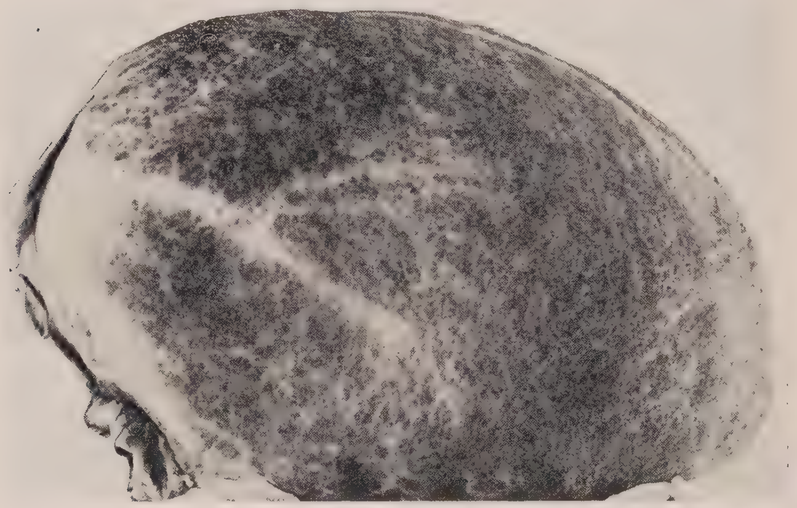

Fig. 380.—Portion of upper surface of Liver in long-standing Biliary Cirrhosis, showing the fine granularity.

Case of obstruction of common bile-duct by calculus.

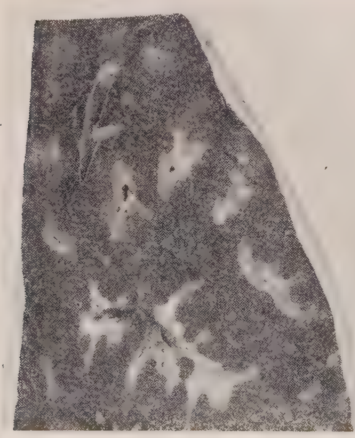

Fig. 381.—Portion of Liver in Bilharzial Cirrhosis, showing the pale areas of fibrous Tissue around the Portal Tracts. × $\frac{4}{5}$.

largement. There is no evidence that the cirrhosis results from accumulation of the hæmosiderin,—in fact, it precedes the latter; and the etiology of the condition is still obscure.

Suppurative Hepatitis—Abscesses in the Liver. The liver may become infected with pyogenic organisms, either (*a*) by the blood stream, or (*b*) by the biliary passages; and blood infection may take place either by the arterial or by the portal blood.

(*a*) *Blood Infection.* Abscesses due to a *general* blood infection are usually of the type of miliary abscesses, though they are not nearly so common or so numerous as in the kidneys. They are met with especially in suppurative osteomyelitis and periostitis. Abscesses of larger size produced by actual embolism are occasionally met with in pyæmic conditions. In new-born infants infection may reach the liver through the umbilical vein. In such cases multiple abscesses may be present in the liver substance.

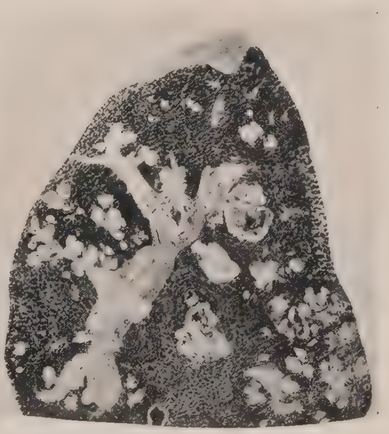

Fig. 382.—Section of Liver, showing *Pylephlebitis suppurativa* and numerous small Abscesses. × $\frac{2}{3}$.

In the majority of cases, however, blood infection occurs through the *portal* circulation, e.g. in cases of appendicitis, gastric ulcer, intestinal ulceration, and occasionally from malignant disease. In some cases embolism is the method of infection, and a single abscess or multiple abscesses may form. In others, however, there is a spreading thrombosis from the lesion to the liver, with secondary suppuration of the thrombus—the condition being known as *pylephlebitis suppurativa* (Fig. 382). The process extends along the branches of the portal vein, and strands of suppuration surrounded by groups of abscesses form in the liver, some parts being more affected than others. At a post-mortem examination of such a case, the track of suppuration can be readily traced by slitting up the portal vein, which contains suppurating thrombus, and then following the process downwards.

Tropical abscesses are produced by the *Entamœba histolytica*, and are a not uncommon complication of amœbic dysentery. In the majority of cases there is a single abscess which may reach a large size; the commonest site is the upper part of the right lobe, where the abscess forms a dome-shaped swelling. It may ulcerate through the diaphragm and discharge into the lung. Sometimes there are several abscesses, but they are rarely numerous. Although the term 'abscess' is usually employed, the lesion is of the nature of necrosis of the liver tissue followed by softening, rather than a true suppuration. When fully formed, a tropical abscess is enclosed by a distinct capsule, and the contents are a thick glairy fluid, often chocolate-coloured or showing definite admixture of blood. On microscopic examination of the contents, there are found chiefly necrotic liver cells, granular débris, and a varying number of red corpuscles ; a few leucocytes may be present, but the material has not the characters of pus. Bacteria are usually absent, though sometimes secondary infection by them occurs. The entamœbæ have a necrotic action on the liver cells similar to that seen in the case of the intestine (p. 561). At an early period they may be present throughout the necrotic material, but they soon die out, and when the abscess is encapsulated they are present only in the inner layer of the granulating wall. Accordingly, when a liver abscess is opened, no entamœbæ may be discoverable in the evacuated contents, but they may be found at a later period when they are separated in the discharge from the wall.

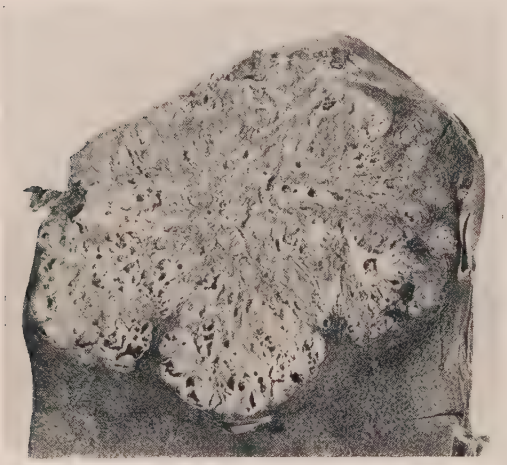

FIG. 383.—Actinomycotic Abscesses in Liver, showing the characteristic loculated arrangement. × $\frac{2}{3}$.

In *actinomycosis*, secondary abscesses in the liver are of not uncommon occurrence, especially when the primary lesion has been in connection with the large intestine or appendix. The suppurative process is of subacute character and encapsulated, and the abscesses in the early stage of formation are arranged in small groups, presenting a honeycomb appearance (Fig. 383). Later they may form much larger cavities by confluence. The pus is usually somewhat thick and of a greenish-yellow colour, and in it may be found the small granules or colonies of the actinomyces, which are usually most distinct in the earlier lesions. The colonies, which are of about the size of small pin-heads, may be yellowish in tint, or greenish grey and rather transparent. They may be readily detected by spreading some of the pus on a glass slide and looking at it by transmitted light. If a colony be broken down and stained by Gram's method, the branching filaments of the organism will be readily recognised.

(*b*) *Biliary Infection.* This signifies an ascending infection of the biliary passages, and occurs especially in cases where there is some obstruction of the main bile duct, notably by a gall-stone. The passages become infected by organisms, especially by the B. coli, and there follows an ascending suppurative cholangitis. This in time reaches the liver substance, and its tissue becomes beset with the groups of suppurative or necrotic foci, which afterwards may run together. The pus in the abscesses is bile-stained, and the state of the bile-ducts demonstrates the nature of the condition. The liver tissue is often of a dark olive-green colour, from long-standing jaundice.

In abscesses of the liver the suppuration may reach the surface, the bacteria may infect the peritoneum, and a general or localised peritonitis may be set up, the latter being sometimes in the form of a subphrenic abscess. Adhesions between the liver and the diaphragm may form and then ulceration may occur into the lung, the pus being discharged by the bronchi. Such an occurrence is not uncommon in cases of tropical abscess, and we have met with it in a case of biliary abscesses.

SPECIFIC INFLAMMATIONS

(A) **Syphilis.** The liver is frequently affected in syphilis, both in the congenital and acquired forms of the disease. The lesions are essentially of the same nature in the two, but in the former they are usually of diffuse and of cellular character owing to the large number of spirochætes present, whilst in the latter they are of more chronic nature and more localised. In *congenital syphilis*, the commonest lesion is an extensive proliferation of connective tissue cells in the organ, not only along the portal tract but also throughout the lobules. The growth, which is often remarkably uniform, occurs between the capillary endothelium and the liver cells, and both are pressed on. Thus in a section, the columns of liver cells are seen to be atrophied and somewhat broken up, and are separated by a spindle-celled tissue in which mononuclear leucocytes and lymphocytes are interspersed (Fig. 384). Occasionally compensatory hypertrophy may be

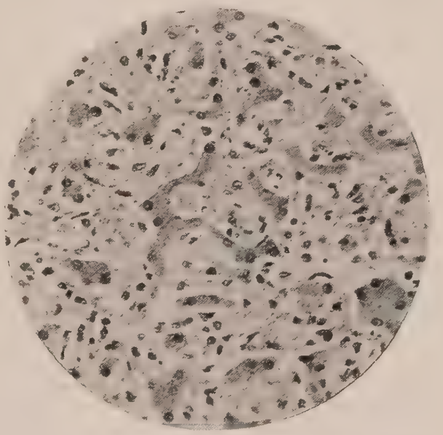

FIG. 384.—Congenital Syphilitic Cirrhosis of the Liver, showing young connective Tissue spreading diffusely between the columns of Liver Cells which are becoming atrophied. × 250.

present at places, some of the liver cells being enlarged and multinucleated. *Miliary gummata* are not uncommon and represent foci where the action of the syphilitic virus has been more concentrated. These are minute cellular nodules with evidence of degeneration or necrosis, and in the centre one often finds what may be recognised as the hyaline remains of necrotic liver cells in process of absorption (Fig. 385). In accordance with the diffuse character of the histological changes, the surface of the liver remains comparatively smooth. The organ is merely enlarged, firmer than normal and often paler, occasionally slightly jaundiced; whilst the lobules are indistinct or unrecognisable, and sometimes a mottled appearance is noticeable. Miliary gummata, when present, are seen as minute points of paler appearance, but those of smallest size can be found only on microscopic examination. In a small proportion of cases the cirrhotic change occurs more in the form of fine bands of connective tissue, chiefly related to the portal tracts, and such a condition, in cases which survive, may give rise to nodular cirrhosis at a later stage. Occasionally large gummata of the ordinary type occur as a result of congenital syphilis, but this is a rare condition. As already stated, spirochætes are usually abundant throughout the liver in congenital cirrhosis, but in many cases they are numer-

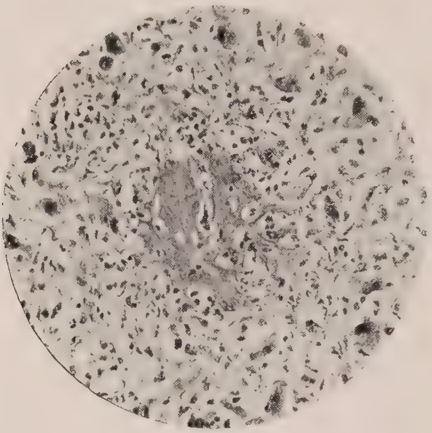

Fig. 385.—Miliary Gummata in congenital Syphilitic Cirrhosis, showing necrotic Centre with connective Tissue proliferation around; also remains of Liver Cells. (Prof. C. H. Browning.) × 200.

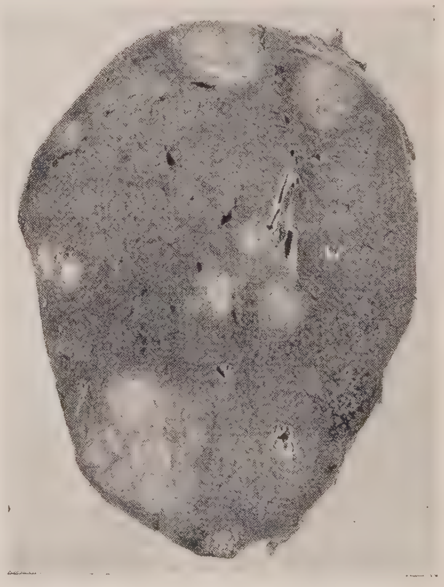

Fig. 386.—Multiple Gummata of Liver, showing the characteristic necrotic Centre with fibrous Capsule. × ½.

ous apart from cirrhotic change, and all degrees of connective tissue proliferation are met with. The lesions of congenital syphilis in the liver are often associated with corresponding changes in the lungs and pancreas.

In *acquired syphilis* the chief lesions are gummata and irregular cirrhosis. Gummata are comparatively common and may reach a considerable size, especially when a mass is formed by confluent nodules, as sometimes happens. They may be single or multiple, and may be found at various stages. In the early stage they are usually somewhat rounded in form and may be reddish grey in colour, usually with varying degrees of central necrosis, whilst at a later stage they are necrotic and yellowish and are encapsulated by fibrous tissue (Fig. 386). Gummata have a special tendency to undergo absorption, and fibrous cicatrices are brought about in this way. Fibrosis may occur, however, apart from gummata, usually in irregularly distributed bands. Partly as the result of the absorption of gummata, and partly owing to the cirrhotic condition, the syphilitic liver is often intersected with coarse bands of connective tissue, which lead to indrawing of the surface at places, and thus to great deformity of the organ. Sometimes a portion at the margin of a lobe may be almost cut off from the rest by connective tissue. This type of lesion—known as the *hepar lobatum*—may be regarded as practically characteristic of syphilis (Fig. 387). Here also compensatory changes occur, and the liver tissue forms rounded projections between fibrous bands. The condition is often accompanied by chronic perihepatitis with adhesions. Amyloid disease, sometimes irregular in distribution, may be present in the liver along with the syphilitic lesions.

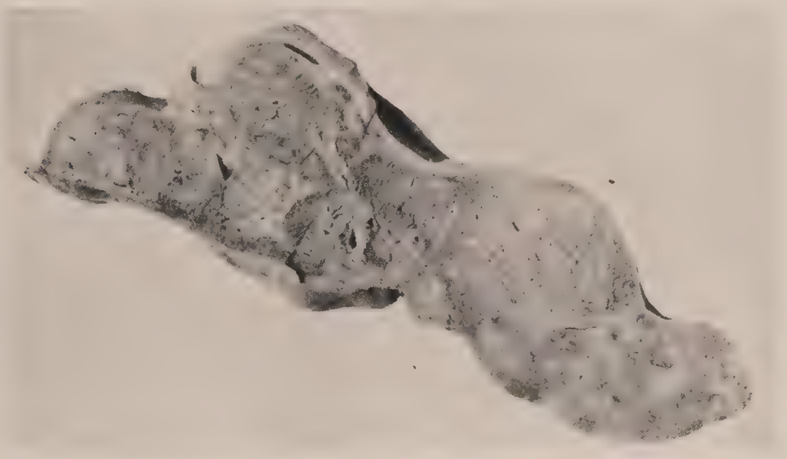

FIG. 387.—Section of Liver, showing great Deformity resulting from chronic Syphilitic Cirrhosis.

(B) **Tuberculosis.** Tuberculous lesions, which are less common than in most other organs, are of two types. In the first place, miliary tubercles occur in the liver in general tuberculosis. The nodules, which are found chiefly in the periportal tissue and in the capsule, may be of very minute size and scarcely recognisable by the naked eye, or they may be larger and more distinct. In the latter case, the centre is usually caseous and shows bile staining. Apart from this generalised condition, a few nodules of more chronic nature may be caused by bacilli borne by the blood stream from chronic lesions in other organs. The presence of large, almost tumour-like tuberculous masses in the liver has been recorded in a few cases, but the occurrence is very rare. Such lesions may resemble gummata very closely and can be definitely identified only by the finding of tubercle bacilli. The second type, known as bile-duct tuberculosis, is of rare occurrence. In this form there occur comparatively large tuberculous nodules in groups, and the central parts may become softened so that small cavities are formed ; a considerable part of the liver may be involved by such lesions. The condition represents a spread by the bile-ducts and the caseous material is stained with bile. There is doubt as to the exact mode of origin, but most probably a tuberculous nodule in the liver substance ulcerates into a bile-duct within which, as well as by the lymphatics, the bacilli then spread.

(C) **Actinomycosis.** This has already been described in connection with the suppurative lesions (p. 610).

PARASITES

Hydatid Disease. As the liver is the commonest site of hydatid disease in the human subject, a short account may here be given. A hydatid or echinococcus is the cystic stage of the *Tænia echinococcus*, and infection is got from the dog, in which the strobilus or worm stage exists. The commonest type of hydatid is a cyst of large size in the interior of which there are secondary or daughter cysts, and sometimes within these again grand-daughter cysts. The cyst wall consists of a laminated ectocyst of chitinous substance, and an endocyst which is a cellular or parenchymatous layer. In the endocyst, small cysts or brood capsules are formed, and within them numerous scolices with double rows of hooklets develop ; these scolices are seen either in an invaginated or non-invaginated condition. The contents of the cyst are a clear, almost colourless fluid, in which there is a considerable amount of sodium chloride, some protein (little of which, however, is coagulable by heat), a small amount of glucose, etc. When a cyst is punctured and the fluid drawn off, one usually finds in it some scolices or separated hooklets, and thus a diagnosis may be made (Fig. 388). The daughter and the grand-daughter cysts have the same structure as the mother cyst, and in them the brood capsules may or may not be developed. When the parasite dies, the fluid becomes absorbed and the cyst wall becomes collapsed and disintegrated, and later is not infrequently the seat of calcification. It is to be noted that in a dead hydatid the hooklets persist and are recognisable for a long time. Sometimes there is secondary infection by pyogenic organisms and suppuration occurs.

The fluid of a hydatid cyst is believed to have certain toxic or irritating properties, which are manifest when rupture occurs into the peritoneum. Absorption of proteins from a hydatid evidently takes place, as antisubstances appear in the blood of those infested with hydatids. These antisubstances act both as precipitins and also as deviators of complement, when the serum (antisubstance) and the hydatid fluid (antigen) are allowed to interact (p. 189).

The common hydatid just described is known as *Echinococcus hydatidosus* and may reach a large size, sometimes being as big as a man's head; occasionally more than one hydatid may be present. Sometimes a single simple cyst in which brood capsules are present is met with, but no daughter cysts; this is called *Echinococcus simplex*. Another type of hydatid is the *Echinococcus multilocularis* or *alveolar hydatid*. This occurs in the form of a mass of small cysts, most of which are not more than ¼ in. in diameter, and which are separated by the connective tissue of the host. It has thus a honeycomb or alveolar structure. Its consistence is somewhat gelatinous and the outer surface somewhat nodular. It has been compared to a colloid cancer and, as a matter of fact, it has been often mistaken for a tumour. The walls of the cysts are composed of thin ectocyst and endocyst, and brood capsules are formed in the interior of some of them. Others show various stages of degeneration and are often surrounded by giant-cells. As the mass of cysts increases in size the central part often undergoes necrotic softening.

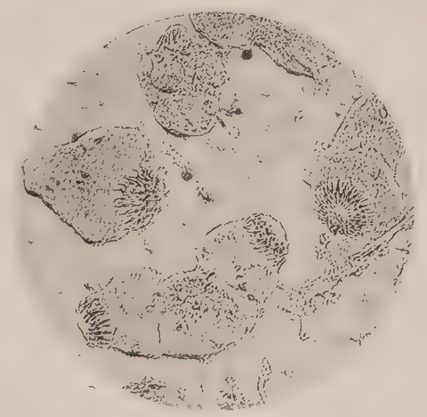

Fig. 388.—Scolices of *Tænia echinococcus* in fluid removed from Hydatid Cyst of Liver.

Note the characteristic rings of hooklets. × 100.

There has been considerable dispute as to the significance of the *Echinococcus multilocularis*. Its peculiar structural arrangement, certain morphological differences in the hooklets, and a different geographical distribution from the ordinary hydatid, are in favour of the view that the parasite is a distinct species or at least variety; but this does not seem to be definitely settled.

The adult worm, *Tænia echinococcus*, which usually occurs in the intestine of the dog, is of small size, measuring only 3–6 mm. in length. The small head has a rostellum with two rows of hooklets and there are four suckers. There are only three or four segments, and the terminal one, which is much the largest, contains the genital glands. The eggs, which are about 35 μ in diameter, have a distinct covering or embryophore with radial striation. When the eggs are swallowed by man or by some animal, the covering of the ovum becomes dissolved and the minute embryo or oncosphere, which possesses three pairs of small spines, bores its way into the blood vessels of the alimentary canal and passes to the liver or other organ. The oncosphere there enlarges and a space containing fluid forms in its centre, whilst the peripheral part becomes differentiated into ectocyst and endocyst, and then the formation of brood capsules follows.

Other Parasites. Species of *Distoma—D. hepaticum, lanceolatum,* etc.—sometimes invade the bile-ducts and give rise to jaundice ; such an occurrence, however, is very rare in this country. The *Schistosoma hæmatobium* occasionally lodges in the portal branches in the liver, and the discharge of ova into the surrounding tissue produces a form of cirrhosis (p. 608) ; this lesion is met with in Egypt and other countries where the parasite abounds. Occasionally small fibrous nodules, which may reach the size of a pea, are produced by the *Pentastoma denticulatum*, which is the larva of a small arthropod, *Linguatula rhinaria*, the adult form occurring in the nasal cavity of dogs, rarely of man. Such nodules are fairly common in certain districts on the Continent ; they are met with especially under the capsule of the liver, and the central parts are often occupied by degenerated and calcified material, in which the dead parasite may still be found. Infestation with the *Coccidium oviforme*, common in the rabbit, has occasionally been observed in the human subject, but is very rare.

TUMOURS

Simple tumours of the liver are of rare occurrence, the commonest being the *adenoma* and the *cavernous angioma*. The adenoma is met with in the early years of life, and is probably always of congenital origin ; it may be single or multiple. It is round or oval in form and usually well circumscribed. Its substance is generally paler than the surrounding liver tissue, although red vascular areas may be present ; sometimes the growth forms bile-pigment and its tissue has thus a greenish tint, while the rest of the liver has a normal colour. The tumour is usually comparatively small, but we have met with a specimen of localised growth which was of the size of a small coco-nut, and we have seen a considerable part of the liver occupied by irregular adenomatous formation, distinctly bile-stained. In most instances the tumour is composed of trabeculæ of liver cells, but the arrangement is somewhat irregular and usually no bile-ducts are present ; the growth is thus a *hepatoma*. Occasionally such a tumour assumes malignant properties, even at an early period of life. When the original hepatoma has been bile-stained, the malignant growth may be free from pigment or slightly coloured. The hypertrophic nodules seen in multiple nodular hyperplasia (p. 599), and other conditions where there has been destruction of the liver tissue, are not to be regarded as tumours, though they are sometimes described as adenomata. Adenomata composed of bile-duct epithelium have been described, but are very rare. The cavernous angioma (p. 216) is fairly common in the liver. It has a dark purple colour owing to the contained blood, and is sharply demarcated from the surrounding tissue. Although probably starting from a congenital abnormality, the angioma apparently undergoes gradual increase in size, and it is usually met with in the later years of life.

Of the *primary malignant growths*, cancer originating from the liver cells is of most importance. Occasionally a congenital hepatoma assumes malignant characters even in childhood, but, in the great majority of cases, a liver-cell cancer is preceded by cirrhosis of the liver. Occasionally the growth forms a single large mass which may appear to be encapsulated—'massive cancer'—the central parts of which are often partly necrotic and hæmorrhagic (Fig. 389). In other cases several nodules are present, and there is further the type in which an extensive nodular infiltration is present in a considerable part of the liver. The growth is, as a rule, confined to the liver, though it often grows into the branches of the veins of the liver; occasionally metastases occur in the lymphatic glands and elsewhere. There has been considerable discussion as to the relation of cirrhosis and cancer, but we believe that the cancer develops secondarily to the hyperplastic process which goes on in the liver cells in cirrhosis, the compensatory proliferation, for some reason, becoming of malignant and infiltrative type (p. 269). The cells of the tumour are undoubtedly derived from liver cells (Fig. 390), and the arrangement of the latter is more or less of the trabecular type; ultimately, irregularities in arrangement and aberrant forms appear (Fig. 391). Another point is, that this malignant transformation may occur in several independent foci, so that there is sometimes an appearance as if many individual lobules were becoming transformed into cancer. Primary carcinoma of the liver is also met with occasionally in the cirrhosis of hæmochromatosis, this occurring in approximately the same proportion of cases as in ordinary cirrhosis.

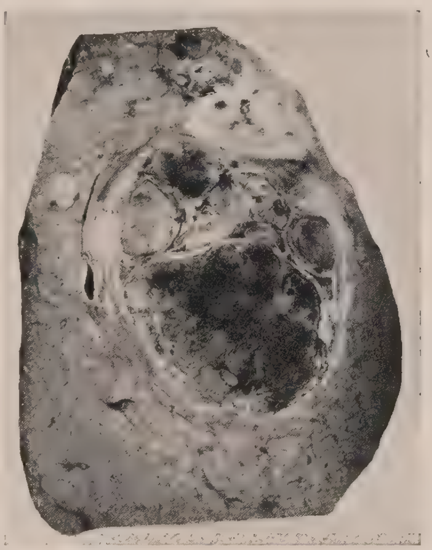

FIG. 389.—Primary Carcinoma in a Cirrhotic Liver.

The growth is chiefly in one large mass which is partly necrotic.

Primary cancer derived from the smaller bile-ducts and having the structure of adeno-carcinoma also occurs, but is rarer than the above variety; we have met with a case where the epithelial cells were narrow and almost spindle-shaped, like the epithelium of newly formed bile-ducts, as seen in cirrhosis and other conditions. Bile-duct carcinoma also has been observed to originate in cirrhotic livers.

An important fact is that cancer of the liver can be experimentally produced in animals by various carcinogens. Orr, for example, found that the growths set up by 'butter yellow' might be liver cell carcinoma, bile-duct carcinoma or bile-duct cystadenoma. I can confirm this in the case of other carcinogens used by Kennaway, from the examination of specimens which he has kindly given me.

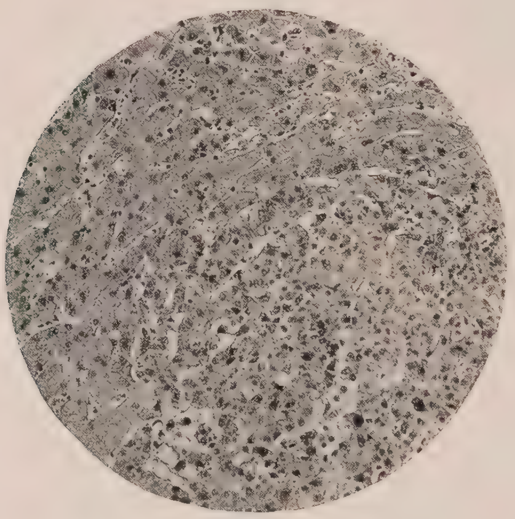

Fig. 390.—Early stage of Cancerous change in a case of Cirrhosis.

The cancer, seen in lower part of figure, has originated in a hypertrophic focus and its cells are seen to be continuous with the columns of liver cells. × 100.

Primary sarcoma of the liver is much less common than primary cancer. In fact, it is of very rare occurrence. There is usually one main mass of growth, but smaller nodules may be present around and great enlargement of the organ may result.

Secondary Tumours. The liver is a common site of secondary growths of all kinds. In carcinoma of the stomach the occurrence of secondary growths may be said to be the rule, either early or late (p. 546). Secondary cancer may be in one or two main masses, but usually the whole organ is permeated

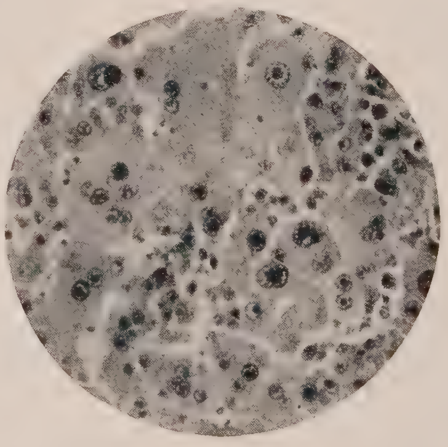

Fig. 391.—Portion of primary Carcinoma of Liver, secondary to Cirrhosis.

Note the resemblance to liver tissue, though aberrant cells are present. × 250.

with nodules of the growth (Fig. 392). The liver becomes enlarged and its surface is beset with nodular elevations, some of which may show umbilication owing to contraction of the stroma. In cases of the encephaloid variety, the liver may be enormously enlarged and may weigh seven or eight pounds, or even more; the individual masses are sometimes huge and often show necrotic change in their centres. A certain amount of jaundice may result from implication of numerous bile-ducts, or sometimes there may be complete obstruction of the bile-duct owing to pressure of a growth in the portal fissure. Sometimes, however, there are very extensive metastases without jaundice. Secondary sarcomata are not uncommon and the liver may undergo great enlargement. In cases of melanotic growth, secondary nodules in the liver may occur in enormous numbers; most of the nodules are of an almost jet-black colour, but some of the smaller may contain less pigment and be comparatively pale. Secondary nodules of chorion-epithelioma are frequently present in the liver. They are usually of a round form and have a markedly hæmorrhagic character (Fig. 393). The liver is also frequently extensively invaded by secondary

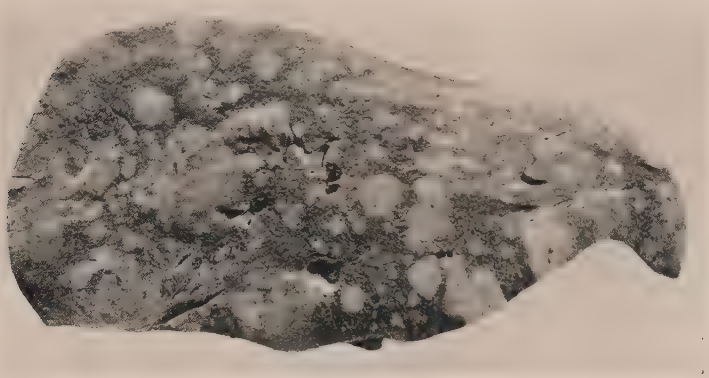

Fig. 392.—Multiple secondary Nodules of Cancer in Liver.

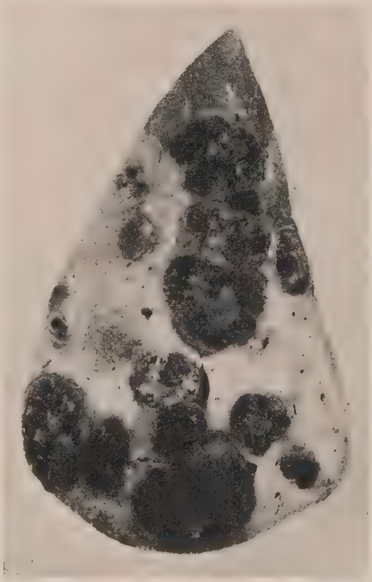

Fig. 393.—Multiple Nodules of secondary Chorion-epithelioma in the Liver.

Note the hæmorrhagic character.

growths of sympathicoblastoma and other malignant tumours (p. 256).

Cystic Liver. Cysts of congenital origin are found in the liver, and in such cases there is usually present cystic disease of the kidneys; the latter condition, however, often occurs without any affection of the liver. The cysts vary greatly in size and in number; there may be only a few, or the liver may be studded with them. They usually contain a clear albuminous fluid and have a somewhat cubical epithelial lining. They are supposed to originate in connection with the bile-ducts, but the mode of formation has not been ascertained. It is unknown too why the kidneys and liver should be so frequently involved at the same time. It may be noted, however, that in some cases other congenital abnormalities, such as hydrocephalus, spina bifida, etc., may be present.

THE GALL-BLADDER AND BILE-DUCTS

The normal function of the gall-bladder is of importance in relation to its pathology. It is now known that the gall-bladder is not only a reservoir for the bile but has an important action in concentrating it. The relatively watery bile from the liver may be reduced to about one-tenth of its volume by the absorption of water and salts, and, with the addition of a certain amount of mucin from the lining of the gall-bladder, it assumes the somewhat thick and mucoid character of gall-bladder bile. This concentrated state of the bile comes to be of importance in connection with the formation of gall-stones. It has also been established by clinical and experimental methods that the gall-bladder practically never empties itself completely. When the acid chyme enters the duodenum the gall-bladder discharges a certain proportion of its contents, and thereafter only small quantities are passed at intervals; but there is always a relatively large amount of bile retained in the gall-bladder. Between these periods of discharge the bile from the hepatic ducts probably enters the bladder in a fairly steady flow, there to be concentrated. When the gall-bladder is removed a certain amount of dilatation of the extra-hepatic ducts—common bile-duct and hepatic ducts—is usually observed, and this indicates an action of the sphincter of Oddi at the lower end of the common bile-duct. It seems doubtful, however, whether the normal intermittent flow of bile into the duodenum is effectively restored in this way. It is possible that this dilated state of the common bile-duct may predispose to an ascending infection, as some consider, but there is no evidence that this is of frequent occurrence. In any case, removal of the gall-bladder is usually not attended by any distinct disturbance.

Obstruction of Passages. Obstructive lesions are of common occurrence and it has long been known that the biliary passages above an obstruction are filled usually by dark concentrated bile, but sometimes by colourless bile—the so-called 'white bile.' Experimental work, especially that of Rous and McMaster, has shown that the difference depends upon the position of the obstruction. If this is below the junction of the cystic duct with the hepatic duct (the commoner site) the concentrating action of the gall-bladder is available and the bile becomes thickened and of dark colour. If, on the other hand, the obstruction is above the junction the bile cannot be concentrated and its secretion soon stops; the bile pigment, cholates, etc., are gradually absorbed and the fluid may become practically colourless. And it is a striking fact that even in a jaundiced animal this secretion from the lining of the ducts does not contain bile pigment, in this respect resembling the saliva, tears, etc.

On going through our pathological reports I find that the facts recorded correspond well with these results. Fig. 401 shows great dilatation of the bile-ducts within the liver; they were filled with colourless bile and the condition was due to a cancer of the cystic duct which had led to obstruction also of the hepatic duct. In most cases, however, the obstruction is below the entrance of the cystic duct and accordingly the bile passages are filled with dark olive-green bile. The darkest and thickest bile is met with when the obstruction below the cystic duct is partial or intermittent.

It may be noted further that, when the wall of the gall-bladder is diseased, its absorptive and concentrating power is lost to a varying extent and, when it is entirely in abeyance, the result may be the same as if there were no gall-bladder present; in this case accumulation of relatively colourless bile in the ducts will be the ultimate result.

The *cystic duct* is sometimes obstructed owing to impacted stone or to some other lesion involving the neck of the gall-bladder, and the latter may be distended by a clear mucoid fluid—*mucocele* of the gall-bladder. The biliary constituents become absorbed and a mucin-containing fluid is formed by the lining of the bladder. In such cases there is usually evidence of previous inflammatory change in the bladder wall, and this probably explains the difference from the result of experimental obstruction. Ligature of the cystic duct in a healthy animal is not followed by distension; the gall-bladder becomes rather shrunken and contains highly concentrated gelatinous mucus (Aschoff).

Cholecystitis. Inflammation of the gall-bladder is produced by bacteria, chiefly pyococci and bacilli of the coli-typhoid group; of the former non-hæmolytic streptococci are most frequently concerned. The organisms usually reach the bladder by the blood stream, being carried directly to the wall. It is possible that infection may come by the bile from the liver when the organisms are present there, as in typhoid fever. An ascending infection from the duodenum can hardly occur apart from some other lesion, obstruction, cholangitis, etc. It is often impossible to state the path of infection in any individual case, but direct conveyance to the gall-bladder has been demonstrated experimentally, the cystic duct being tied and then the organisms introduced into the blood stream; cholecystitis has in this way been set up. Accordingly, bacteria may be carried in a similar way to the gall-bladder wall from other infected foci such as dental caries, lesions of throat, etc. It has also been found in clinical cases that organisms may be cultivated from the gall-bladder wall or from the cystic lymph gland when the bile is sterile.

Infection by the typhoid or paratyphoid bacilli frequently occurs by the blood stream, and the organisms may persist for a long time with little or no inflammatory change resulting. The formation of gall-stones may follow, and this takes place especially when there is catarrh, which is often associated with the additional presence of B. coli.

Acute cholecystitis may be of various types. It may be merely catarrhal, fibrinous or pseudo-membranous, hæmorrhagic, or suppurative. In severe cases, which are met with especially when the cystic duct is obstructed, abscesses may form in the wall, or there may even be necrosis or gangrene of the wall with rupture into the peritoneal cavity. Apart from the latter occurrence, local infection of the serous surface is not uncommon, and adhesions around the gall-bladder are thus often produced. Occasionally the outlet becomes blocked and an accumulation of pus occurs, leading to empyema of the gall-bladder. Ulceration of the mucous lining is a frequent result; this may pass into a chronic stage and lead to great fibrous thickening.

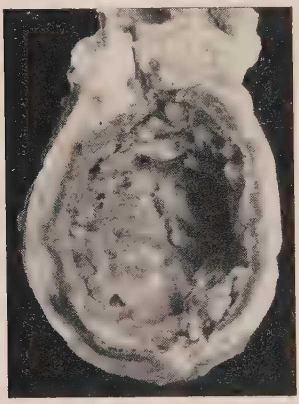

Fig. 394. — Chronic Cholecystitis, showing great thickening of Wall with pocket formation in lining. The gall-bladder was packed with small rounded Stones. Natural size.

Chronic cholecystitis is usually an insiduous infection often accompanied by symptoms of gastric disturbance; sometimes it may be traced to a previous acute attack. Again, an acute attack may occur as an exacerbation in a chronically inflamed gall-bladder. The appearances of the wall vary according to the presence or absence of gall-stones and according to the presence or absence of obstruction, but the all-important change is interstitial, resulting in fibrous increase. When there is obstruction the bladder may be dilated and its wall thinned and smooth; otherwise it usually shows distinct and sometimes great thickening with opacity of the wall (Fig. 394). The lining is often irregular or has a reticulated appearance, and there may be distinct pouches especially when numerous gall-stones are present. The contents may be clear or turbid or distinctly purulent. In a considerable proportion of cases of chronic cholecystitis the bile is sterile, but in many of these organisms can be cultivated from the wall of the gall-bladder. A common result of chronic cholecystitis is the formation of multiple gall-stones, as is described below, and some of the most serious complications result from their presence.

In chronic ulcerative cases there occurs, in association with the process of healing, great irregularity of the mucin-forming glands, and these may be situated deeply, even between the muscle bundles. It is important to note that in this way an appearance suggestive of malignant infiltration may be produced, although no tumour growth is present. Sometimes the epithelial growth is considerable and numerous gland-like spaces lined by epithelial cells are present in the inner part of the wall, which is thickened and fibrous. The term 'cholecystitis glandularis proliferans' has been applied to such a condition.

Cholesterosis of Gall-bladder. It would appear that under normal conditions a certain amount of absorption of cholesterol takes place from the gall-bladder. In certain states, however, this process becomes exaggerated and cholesterol, in combination as doubly refracting esters, becomes deposited within the histiocytes in the mucosa, a condition of *cholesterosis* resulting; the lipoid is seen also in the deepest parts of the epithelial cells. This deposit occurs in patches and there may thus result distinct yellowish spots visible to the naked eye, a speckled appearance of the mucosa being produced (Figs. 395, 396). The term 'strawberry gall-bladder' has been applied to the condition, and this term is appropriate when the mucosa is much congested and the spots stand out on a red background; but often there is no congestion or any other change. Further, as shown by Wilkie, the lipoidal deposits may increase in size, forming small polypoidal nodules; these may occasionally become free and form centres around which cholesterol is deposited. The deposit of cholesterol in the mucosa seems to depend chiefly on metabolic changes leading to excess of cholesterol in the blood and thus in the bile. It is met with apart from inflammatory changes, though the latter is believed by some to intensify the process. The condition is often met with in gall-bladders otherwise normal. Its importance is that it is often

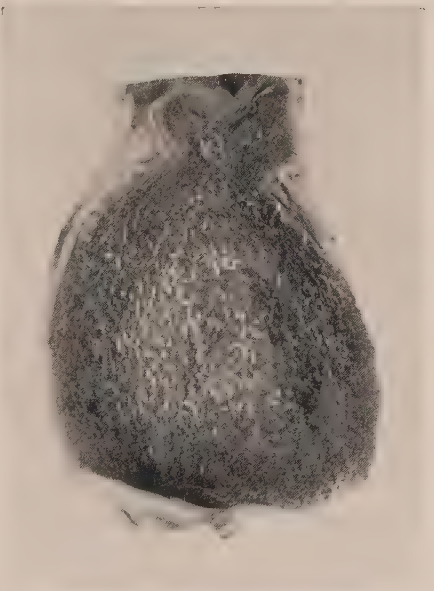

Fig. 395.—'Strawberry Gall-bladder,' showing characteristic marking due to deposit of cholesterol esters.

associated with the formation of cholesterol stones, solitary or mulberry. These are present in about 30 per cent. of cases of cholesterosis (Mackey).

Tuberculosis of the gall-bladder with ulceration has been described, but it is very rare.

Gall-Stones. These are concretions formed from constituents of the bile—chiefly cholesterol, bile pigments and lime salts—in varying proportions in different cases, along with a certain amount of organic material. Their site of formation is the gall-bladder, but sometimes in a dilated hepatic duct or its branches there may form somewhat columnar concretions of crumbling consistence, composed mainly of bile pigment (Fig. 397). Occasionally also small and more compact stones of dark colour and composed chiefly of bile pigment are found in dilated ducts.

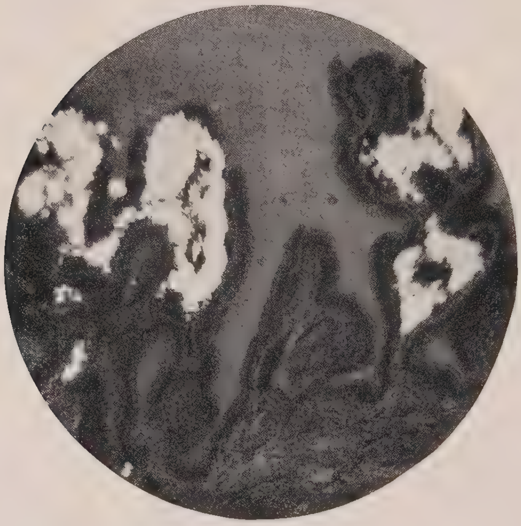

Fig. 396.—Section of wall of 'Strawberry Gall-bladder,' showing deposits of cholesterol fat in papillæ, viewed by polarised light. (Mr. W. A. Mackey.) × 75.

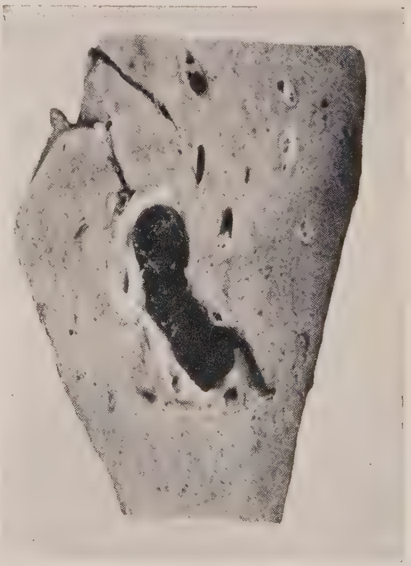

Fig. 397.—Intrahepatic Gall-stone, lying in dilated duct in liver. × ¾.

The following are the chief types of gall-stones met with in the gall-bladder :—

(1) The *Cholesterol Stone.* This form, which is as a rule solitary, is usually of oval shape and may reach the size of a small plum. Its colour is pale yellow or almost white; it is somewhat soapy to the touch and is of a low specific gravity, often floating in water when dried. When broken across, it shows a crystalline structure composed of sheaves of

cholesterol crystals which radiate outwards from the centre. The latter is sometimes of dark colour, owing to the incorporation of bile pigment between the crystals, but there is no break in the continuity of the formation and there is no trace of lamination. The stone may thus be regarded as a result of the process of crystallisation. Some specimens of solitary cholesterol stones, however, have a laminated cortex composed of bile pigment and calcium salts, the pigment causing the darker markings (Fig. 398, *b*). This is due to a secondary deposit, which occurs, when the gall-bladder wall becomes inflamed by secondary bacterial invasion. Stones of this class may be called *combination* or *compound cholesterol stones*. They constitute the largest gall-stones met with. As already mentioned, multiple cholesterol stones of mulberry type may be met with. They are usually few in number, but occasionally numerous. The surface of the larger ones is somewhat nodular and on section they show a radiate crystalline structure, there being sometimes a considerable amount of bile pigment incorporated in the central parts.

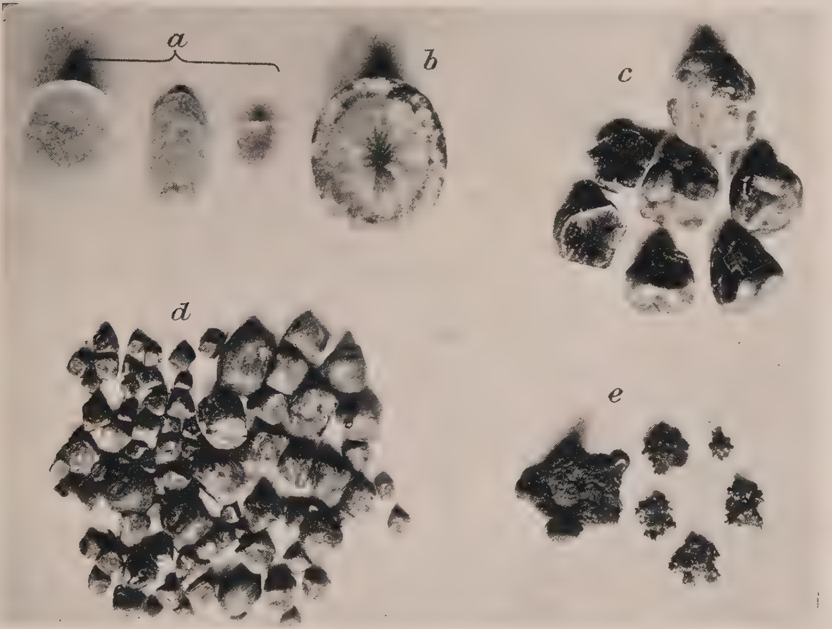

FIG. 398.—Types of Gall-stones.

(*a*) Three cholesterol stones; (*b*) cholesterol stone with secondary pigmented layer—composite stone; (*c*) and (*d*) multiple facetted mixed gall-stones; (*e*) bile-pigment stones. × $\frac{2}{3}$.

(2) The *Mixed or Laminated Gall-stones.* These, which are the commonest type, are multiple and often in great numbers (Fig. 398, *c*, *d*). They are sometimes associated with and secondary to a solitary cholesterol stone. They vary greatly in size—from half-an-

inch or more in diameter to the size of sand grains, are irregular in form and often facetted. On section they have a distinctly laminated structure, dark brown and paler layers alternating. Such stones consist chiefly of cholesterol and bile pigment in varying proportion; the dark layers are composed mainly of bile pigment, the paler mainly of cholesterol, both containing an admixture of calcium salts and a certain amount of organic material. It is seen that in an angular stone the layers are thicker at the angles owing to more abundant deposit in these situations; the facetted character is thus mainly due to the mode of formation of the stone, in which mutual pressure is also concerned. Their colour varies greatly—being grey, brownish yellow, pinkish, brown, or almost black—according to the nature of the covering layer and the stage of oxidation of the bile pigment. Mixed gall-stones occur in very variable numbers; occasionally they may be in hundreds when of small size. They may be free in the bile, which may be mixed with inflammatory exudate or pus, or they may be tightly packed together within a gall-bladder with thickened wall (Fig. 399). Occasionally a small contracted bladder contains two or three barrel-shaped stones placed end to end.

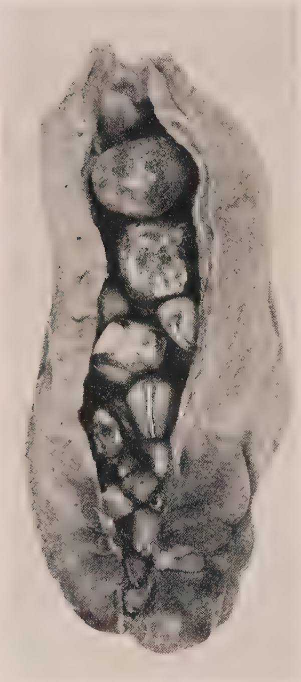
FIG. 399.—Gall-bladder filled with numerous Gall-stones of mixed type. × $\frac{2}{3}$.

(3) *Bile-pigment Stones.* Such stones, which are comparatively rare, are usually multiple, of black colour, irregular in form or occasionally somewhat stellate. They are composed chiefly of bile-pigment. They may be friable or may be of hard consistence. They are often met with in acholuric (hæmolytic) jaundice and are apparently due to excess of bile-pigment in the bile.

(4) *Calcium Carbonate Stones.* These also are rare. They are of small size, pale colour, and somewhat hard consistence.

CONDITIONS AFFECTING FORMATION. Gall-stones are of frequent occurrence, and, while they may give rise to serious effects, not seldom they are unsuspected during life. Especially is this the case with the solitary cholesterol stone. They are commonest in late adult life, especially in those of obese habit, and are much commoner in women than in men; further, they are said to occur more frequently in women who have borne children than in nulliparæ. The three chief conditions concerned in their production are (*a*) *stasis* or *stagnation of the bile*, (*b*) *bacterial invasion* and (*c*) the *composition of* *the bile.* The first condition is produced by an atonic condition of the gall-bladder occurring in association with constipation, which is common in stout women, and is favoured by conditions causing pressure on the gall-bladder. The importance of the composition of the bile has been established by more recent work.

While formerly it was believed that cholesterol was secreted by the mucous membrane of the gall-bladder and ducts, it is now recognised that it is formed in various parts of the body, accumulates in the blood, and is excreted by the liver cells. The cholesterol content of the blood is increased chiefly in pregnancy, obesity, chronic renal œdema, diabetes, etc., and a corresponding increase is met with in the bile. The solitary cholesterol stone forms in a sterile bladder with normal wall, and represents the crystallising out of cholesterol from bile containing it in excess, this of course being favoured by stagnation of the bile and absorption of water. There is also evidence that the amount of bile-salts present is a factor as deficiency of these favours the crystallisation of cholesterol. Such a stone, however, predisposes to bacterial invasion, and thus catarrh, which is attended with extension of mucous glands and a certain amount of exudation, occurs secondarily. Two things may then happen. (*a*) Cholesterol and bile pigment may separate out along with lime salts and form a laminated crust on the surface of the cholesterol stone, producing the combination type of stone; or (*b*) the separation may occur in various independent foci, giving rise to multiple mixed stones. Of course the latter may form in a catarrhal gall-bladder without the presence of a solitary stone, but this probably does not occur apart from the presence of bacteria. These views are well supported by facts; they explain especially the presence together of two so different types as a solitary cholesterol stone and multiple mixed stones (Fig. 400). A mixed stone apparently starts, like concretions elsewhere, around some clump of catarrhal-cells or débris as a nucleus, and the presence of bacteria may often be demonstrated in the centre.

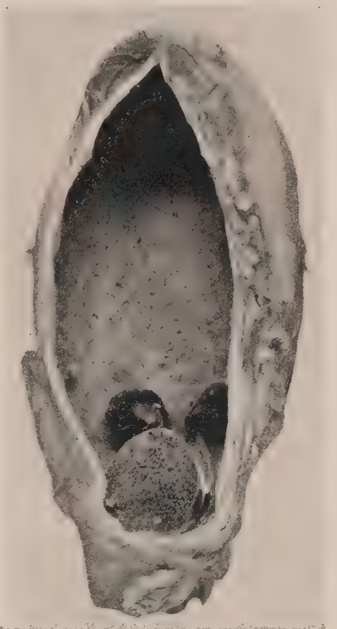

FIG. 400.—Enlarged Gall-bladder with impacted solitary Cholesterol Stone.

Two mixed gall-stones are seen behind. Chronic cholecystitis was present. × $\frac{2}{3}$.

In view of their mode of origin, Aschoff has suitably applied the term 'inflammatory stones' to the multiple mixed stones and the combination stones, and the term 'metabolic stones' to the solitary cholesterol stones and the bile pigment stones.

Effects of Gall-stones. As has been mentioned, the presence of gall-stones, single or multiple, may lead to no noticeable symptoms, but on the other hand, effects of varying severity may follow. These are partly of mechanical and partly of inflammatory character, due mainly to the associated presence of bacteria. The chief of the latter have been described above under cholecystitis (p. 622). A solitary stone may become impacted in Hartmann's pouch next the cystic duct, and great distension of the gall-bladder result; the bile pigments become absorbed and the contents may be a clear mucoid fluid. In other cases when multiple stones are present, the blocking is associated with inflammatory change, and the contents of the gall-bladder are turbid or purulent. If necrosis of the wall occurs, there may be an escape of the contents into the peritoneal cavity.

When cholecystitis passes into a chronic condition, the wall becomes thickened and may be contracted over a mass of closely packed stones. In such a condition there are often adhesions around and a stone or stones may ulcerate in various directions. A large stone of the combined cholesterol type may, for example, ulcerate through into the duodenum or less frequently into the colon. It may be passed along the bowel, but it may become arrested at some part of the small intestine, chiefly by contraction of the muscular coat, and in this way may produce acute intestinal obstruction. Ulceration into the portal vein with the setting up of a pyæmic condition in the liver, has been recorded. A gall-stone may pass into the common bile-duct and give rise to biliary colic attended with jaundice. It may then pass into the duodenum or may be arrested outside for a varying length of time. If, as not infrequently happens, the stone remains loose in the duct the resulting jaundice is often partial or intermittent. If the stone is im-

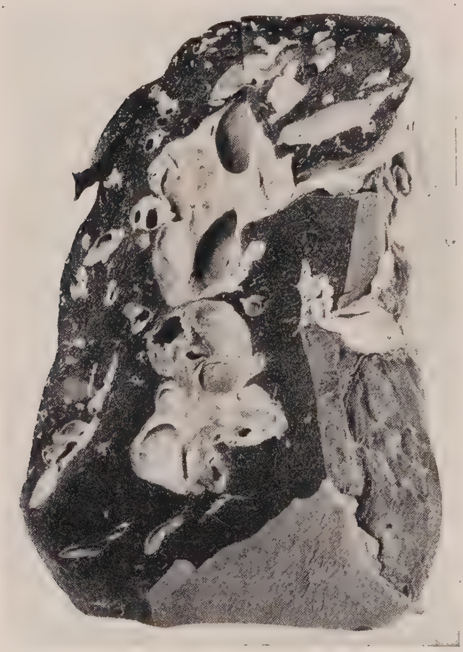

Fig. 401.—Section of Liver, showing greatly dilated Bile-ducts, the result of obstruction due to cancerous growth involving the main Bile-duct. × $\frac{2}{3}$.

pacted the jaundice becomes deep and there is of course complete absence of bile from the stools. The stone may gradually dilate the orifice, or it may be of such size that its passage is effected only by ulceration. Occasionally when the stone is arrested at Vater's papilla bile may pass along the pancreatic duct and give rise to hæmorrhagic pancreatitis. It is to be noted, however, that the symptoms of biliary colic may occur apart from the passage of a stone; they are apparently then due to spasm of the gall-bladder when the outlet is obstructed by inflammatory products.

The presence of a stone often leads to bacterial infection and cholangitis, which may be of suppurative character; and, especially when the stone is impacted, the suppuration may extend backwards to the liver and give rise to biliary abscesses. As has been mentioned, in a comparatively small proportion of cases only does the obstruction of the duct lead to biliary cirrhosis (p. 607). The bile-ducts above an arrested gall-stone or other obstruction sometimes become dilated (Fig. 401) and then effects follow according to the site of the obstruction, as has already been described (p. 621). When the obstruction is below the entrance of the cystic duct there may be a separation out of bile pigment from the concentrated bile, and the formation of secondary biliary concretions, which are usually of elongated form and of comparatively soft consistence.

Lastly, the irritation produced by gall-stones may lead to the development of *cancer*, either in the gall-bladder or in connection with the large ducts. The association of cancer with gall-stones is, however, much commoner in the case of the gall-bladder. Occasionally, when cancer and gall-stones are associated, the latter may be secondary to the cancer, but we believe that the converse sequence of events is the usual occurrence.

Congenital Abnormalities. Minor abnormalities of the gall-bladder which concern its size, shape, mode of attachment to the liver, etc., are not uncommon, but reference need be made only to the important condition of obliteration of the bile-duct sometimes met with at birth. There may be merely a local obliteration or narrowing above the orifice into the duodenum or at a higher level, or, on the other hand, a considerable part of the duct may be absent, and it may be impossible to find any trace even on microscopic examination. The condition of the gall-bladder varies considerably; sometimes the bladder is dilated, sometimes small. It may be absent entirely. There is, of course, complete exclusion of bile from the bowel, with intense jaundice, and death usually follows at an early period. According to some observers the condition merely represents a developmental abnormality, whilst others regard it as the result of inflammatory change. As the result of examination of cases of this condition for Dr. John Thomson many years ago, I came to the conclusion that, in many cases at least, the lesion was the result of a primary congenital defect and not secondary to inflammation. The nature of the condition is, however, still obscure. As mentioned above, in a large proportion of cases biliary cirrhosis is present in the liver.

Tumours. Simple tumours such as fibroma, papilloma, and lipoma, have occasionally been described, but they are all very rare. A papilloma may occasionally reach a considerable size and may lead to obstruction to outflow with much distension of the gall-bladder. *Carcinoma* is comparatively common, and there is no doubt that the presence of gall-stones is an important factor in its causation ; statistics show that gall-stones are present in fully 80 per cent. of the cases of cancer. The growth starts most frequently in the fundus ; next in order of frequency probably comes the region of the neck. It is usually of the slowly-growing infiltrating type, but sometimes it is a soft growth with a tendency to necrosis. Occasionally the gall-bladder may be practically destroyed and its cavity represented by a small irregular space in which gall-stones may be present. It may involve the liver by continuity, or it may give rise to numerous metastases. In the majority of cases the growth is an adenocarcinoma, sometimes a cancer of spheroidal cell or the mucoid type. Squamous epithelioma, arising secondarily to metaplasia of the lining epithelium, also is met with.

Carcinoma occurs besides in connection with the *large bile-ducts*. The two commonest sites are about the junction of the cystic and hepatic ducts and at the lower end of the common bile-duct, the former being more frequent. The cancer is usually a small and slowly growing tumour. Sarcoma of the gall-bladder has been recorded, but the cases are very few.

Jaundice

By jaundice or *icterus* is ordinarily meant the coloration of the skin and other tissues by bile pigment, due to its presence in the blood and tissue fluids. According to the severity and duration of the condition, the skin presents various degrees of yellow staining up to a deep orange colour, and in very chronic cases the tint may become more of an olive-green owing to formation of biliverdin. The internal organs also are pigmented in varying degree, with the exception of the brain and spinal cord which are not affected. In infants, however, some coloration of these may be present, especially in the nuclear grey matter—the so-called 'Kernicterus.' The presence of the pigment in the blood in a marked case is readily shown by the colour of the serum which separates when clotting occurs. The bile pigment is excreted in the urine, which comes to have a characteristic appearance, and also in the sweat ; the tears, however, are not coloured, neither is the saliva, gastric juice or secretion from the bile-ducts (p. 621). When the cause of the jaundice has been removed, the skin may remain coloured for some time after the bile pigment has disappeared from the urine. There is also a rarer condition, further referred to below, in which the skin is coloured but bile pigment does not appear in the urine—*acholuric jaundice*.

The important work of van den Bergh[1] showed that in the normal state there is a very minute quantity (about 1 : 100,000—1 : 400,000) of bilirubin in the blood serum. In various conditions this may be increased without change detectable by the naked eye, and thus jaundice in the clinical sense occurs only when a certain stage of excess of bilirubin in the blood has been reached. Increase of bilirubin in the blood, insufficient to cause recognisable coloration of the skin, etc., is now spoken of as *latent jaundice.* Further, as regards excretion by the kidney, there is a distinct threshold value, excretion of bilirubin occurring when the serum content is about 1 : 50,000. Van den Bergh also established the very important fact that in conditions of jaundice (or more generally, conditions of excess of bilirubin in the blood) the bilirubin occurs in two main forms, as shown by Ehrlich's diazo reaction. When the reagent, a mixture of solutions of sulphanilic acid and sodium nitrite, is added to icteric sera, in some cases a bluish violet colour develops at once—the *immediate direct reaction.* This reaction is given by the bilirubin in the bile and is characteristic of the bile in the blood in cases of obstructive jaundice. In other cases colour appears only after some delay, first a reddish tint which slowly becomes violet—the *delayed direct reaction.* When, however, in a case of delayed or of negative reaction a solution of the serum bilirubin is made in alcohol, a bluish violet colour may develop at once on the addition of the reagent ; this is called the *indirect reaction.* The indirect reaction is given by bilirubin (or hæmatoidin) formed extra-hepatically, e.g. in old extravasations of blood. It is also the distinctive feature of the bilirubin which is not excreted in the urine (p. 637). Another reaction which represents in a sense a combination of the two others is the *biphasic direct reaction.* In this a reddish colour appears at once and then gradually or quickly changes to a bluish tint. This is met with especially in such conditions as catarrhal jaundice, toxic change in the liver, etc., and is apparently due to the presence of both types of bilirubin.

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[1] *Der Gallenfarbstoff im Blute*, by A. A. Hijmans van den Bergh, Leiden, 1918.

Quantitative methods have been introduced for the estimation of bilirubin in the blood ; these give the *total amount.* For details reference must be made to books on methods, but the general principle is treatment of the serum with alcohol which precipitates the proteins and makes *all the bilirubin* available for the reaction. The diazo reagent when added gives a colour change which represents the total bilirubin and this can be estimated colorimetrically against a solution of thiocyanate of iron or of cobalt sulphate. The *unit* represents a 1 : 200,000 solution of bilirubin and corresponds approximately with the amount of bilirubin present in normal human blood.

Icterus index. This is another quantitative method which is much used in America. The blood is allowed to clot and is then centrifuged. The serum is separated and the depth of colour is then estimated colorimetrically against a 1 : 10,000 solution of potassium bichromate. The method is readily applied and has been found of service by many observers but, of course, it does not distinguish directly the two types of bilirubin ; in major degrees of jaundice, however, the type is indicated by the presence or absence of bilirubin in the urine. Further, a yellow colour of the serum may be occasionally given by other substances than bilirubin, such as lutein or carotin.

Van den Bergh came to the conclusion that the bilirubin which gives the *direct* reaction has passed through the liver cells and then been absorbed into the circulation, whereas in the *indirect* reaction the bilirubin is of extra-hepatic origin and has not been acted on by the liver cells. This view accords well with what has been established by recent work with regard to the formation of bilirubin in the reticulo-endothelial system, the liver merely excreting the bilirubin there formed. The direct and indirect reactions in the two main conditions mentioned receive thus a satisfactory explanation. It is also reasonable to suppose that when the liver is damaged there may be two results, viz. on the one hand, failure to excrete bilirubin brought to it, and, on the other hand, a certain amount of obstruction to the flow of bile by damage in the liver parenchyma. Thus both forms of bilirubin may accumulate in the blood and a biphasic reaction may result. Such a view with regard to the relation of jaundice to varieties of bilirubin may be taken at least as the best working hypothesis. Although excess of bilirubin in the blood is taken as an indication of jaundice, the presence or absence of other constituents of the bile, especially the bile salts, has to be considered, and to their presence certain of the symptoms met with in jaundice are due. The cholesterol content of the blood also varies in different types of jaundice, being, as a rule, distinctly raised in the obstructive form.

VARIETIES OF JAUNDICE. In the great majority of cases the cause is some lesion present in the liver or bile-ducts—we may apply the term *hepatic* or *hepatogenous jaundice* to all such cases. Such jaundice, again, may be said to be of two main types. (*a*) In one, there is some evident interference with the passage of bile from the liver to the intestine, with consequent absorption of bile pigments and other constituents—*obstructive jaundice*. (*b*) In the other type there is no such mechanical factor manifest, but, as the jaundice is accompanied by evidence of damage to the liver cells caused by definite chemical poisons or by bacterial toxins in infections, the term *toxic jaundice* may be conveniently applied to it. In some such instances, for example in spirochætal jaundice, the organisms producing the toxins may themselves be present in the liver. When this is the case, the term *infective jaundice* is often applied, but the mode of its production is probably the same as when the jaundice is caused by poisons without the presence of organisms in the liver. It must, however, be recognised that in some cases of toxic jaundice the cause may be actual obstruction of the minute biliary channels; yet the term ‘ toxic ’ is convenient as indicating the primary nature of the condition. It is further to be noted that many poisons which cause toxic jaundice also produce increased blood destruction, and accordingly, whatever view of the process we may take, this increased hæmolysis will tend at least to accentuate the jaundice. In other cases of toxic jaundice, however, there is no evidence of increased blood destruction.

Lastly, in a small group of cases no abnormal state can be found in the liver, and the jaundice apparently depends upon some abnormality in the process of blood destruction. To such cases the term *hæmatogenous* or *hæmolytic jaundice* may be applied. They constitute a small proportion of cases of jaundice, and the staining of the skin is usually of slight degree, whilst bilirubin is absent from the urine.

The provisional classification accordingly is: (1) Hepatogenous jaundice, (*a*) Obstructive, (*b*) Toxic and infective (with or without increased hæmolysis); (2) Hæmatogenous or hæmolytic jaundice. We shall now give some of the main facts with regard to these varieties.

(1) **Hepatogenous Jaundice.** (*a*) **Obstructive.** This may be produced by a variety of conditions. The lumen of the common bile-duct may be blocked by a gall-stone, passing down or impacted, there being then, of course, complete absence of bile in the stools. Infective cholangitis, with or without the presence of gall-stones, may lead to blocking, and it used to be supposed that in ordinary 'catarrhal jaundice' of the sporadic type the obstruction is due to inflammatory swelling of the bile-duct mucosa. Whilst this may be the explanation in some cases, there is evidence that in others, as also in the affection when it occurs in small outbreaks, there is some actual infection of the liver parenchyma with resulting damage. Obstructive jaundice is sometimes the result of constriction of the duct or of pressure on it from outside. Thus cicatricial contraction resulting from old ulceration may produce it, and it is often caused by cancer at the lower end of the common duct or in the head of the pancreas. Also, cancerous or other growths in the portal fissure, enlarged lymphatic glands due to tuberculosis or lymphadenoma, aneurysm, etc., may lead to jaundice by pressure. Then there is a group of conditions in the liver itself—conditions which affect many of the ducts. Jaundice may be occasionally produced in this way by secondary malignant growths in the substance of the liver and also in certain types of cirrhosis as described above, though it is remarkable how in cases of atrophic cirrhosis the minute ducts escape compression and obstruction by the connective tissue. It is to be noted, however, that in cases of cirrhosis without visible jaundice there is often an increase of bilirubin in the blood; that is, latent jaundice is present.

When obstruction of ducts occurs it is quite clear that the liver cells go on forming bile, and this leads to distension of the bile capillaries between the liver cells. In cases of some standing these may be filled with hyaline-looking greenish plugs of inspissated bile, which often show branching processes passing backwards into the substance of the liver cells. If there is chronic obstruction low down, the large ducts also become dilated and the characters of their contents vary according to the position of the obstruction (p. 621). The accumulated bile in the liver contains only a part of the pigment formed, the rest being absorbed and carried into the circulation.

There has been dispute as to the path of absorption. The results of some experiments point to its being by way of the lymphatics; others no less clearly seem to prove that the pigment passes directly into the blood. Whipple and King, for example, ligatured the bile-duct and brought the thoracic duct to the surface so as to make a fistula, and then found that the lymph thus escaping was almost free from pigment, while marked jaundice developed. Probably both paths are concerned in the absorption. It is clear that the bile pigment readily diffuses through the capillary walls into the tissues, and it would be strange if a similar diffusion did not occur from the surcharged liver cells into the related capillaries.

In pure obstructive jaundice, not only is there a great accumulation of bilirubin in the blood with consequent excretion in the urine, but there is also absorption into the blood of bile salts and cholesterol. The bile salts are, as a rule, present in considerable quantity in the urine, though after a time they may disappear; apparently they may cease to be formed by the liver. The cholesterol content of the blood is usually considerably increased, and cholesterol esters are sometimes deposited in the skin so as to form yellow patches of xanthelasma (p. 149).

The absorption of the constituents of the bile leads in itself to comparatively little toxic effect. There is usually a certain amount of slowness of the pulse, with hebetude and mental depression, and itchiness of the skin often occurs. As stated above, in obstructive jaundice the bilirubin in the blood gives the van den Bergh immediate direct reaction. In catarrhal jaundice, already referred to, the reaction varies considerably; at first it is often direct and afterwards becomes biphasic, the indication thus being that obstruction is in part the cause of the jaundice.

Jaundice and Coagulation of the Blood. In jaundice the coagulation time may be lengthened and there is a tendency to bleeding from operation wounds, also delayed healing. This has been ascribed to various factors such as deficient formation of fibrinogen by the liver, fixation of the blood calcium by bilirubin, etc. It has now been shown, however, that the chief factor concerned is a certain degree of deficiency of prothrombin in the blood. The liver is an important seat of formation of both prothrombin and fibrinogen, and necrotic lesions experimentally produced, for example by chloroform, lead to a fall of both substances in the blood, especially of prothrombin. An important advance was by the work of Dam on a hæmorrhagic affection in chickens in which anæmia and a tendency to hæmorrhages were associated with prothrombin deficiency. He showed that this was due to deficiency of a fat-soluble vitamin widely spread in cereals, called by him vitamin K; administration of this raised the prothrombin level and removed the hæmorrhagic tendency. Later it was shown that a naphtho-quinone group formed part of the molecule and various synthetic preparations containing this group have been introduced. The vitamin has now been applied with successful results in various liver conditions, especially in obstructive jaundice and biliary fistula, in which there is prothrombin deficiency. An important point is that the presence of bile salts is necessary for the absorption of the vitamin from the intestine, and thus it would appear that in the conditions mentioned the prothrombin deficiency is the result of want of absorption of the vitamin. Bile salts are accordingly given along with vitamin K in oral administration, or the latter may be used parenterally. Theoretically, vitamin K might fail to remove prothrombin deficiency owing to liver defect, and there is evidence that this is actually the case, e.g. in cirrhosis. Prothrombin deficiency has been observed in other diseases, e.g. in jaundice and anæmia in infants, in steatorrhœa, etc., and can be raised by administration of vitamin K.

(Prothrombin along with calcium and thrombokinase forms thrombin, and this acting on fibrinogen forms fibrin and causes coagulation. The amount of prothrombin in any sample of plasma is calculated from the ‘ prothrombin time ’, that is, the time it takes to cause coagulation along with the three other factors, as compared with a normal plasma. The amount is, of course, in inverse proportion to the prothrombin time.)

Hepatogenous Jaundice. (*b*) **Toxic.** As explained above, we apply this term to the jaundice which occurs apart from gross mechanical obstruction and which depends upon damage to the liver parenchyma. Acute yellow atrophy of the liver and related forms of icterus gravis are outstanding examples. It is met with in various infective conditions, being a prominent feature in yellow fever and spirochætal jaundice (Weil’s disease), where the organisms are actually present in the liver, and it occurs occasionally in typhus, pneumonia, septicæmia, relapsing fever, smallpox, etc. It is seen also in some forms of snake-bite and in poisoning with various definite chemical substances, e.g. trinitrotoluol, phosphorus, salvarsan, etc. In treatment with the last-mentioned substance, it has been found that even when there is no visible jaundice the bilirubin in the blood may be shown by the van den Bergh test to be increased in a certain proportion of cases (Gerrard). This observation is of importance, as increase of the bilirubin calls for care in further administration of the drug.

There has been much dispute as to the nature of toxic and infective jaundice. It should, however, be regarded as likely that the group is not a homogeneous one, that is, that the jaundice is not always produced in one way. Two factors may be concerned. (*a*) In the first place, damage to the liver cells may interfere with the passage of bile along the bile capillaries, in other words to a degree of intra-canalicular obstruction. (*b*) Again as the result of damage, the liver cells may fail to excrete fully bile-pigment formed extra-hepatically. Both factors no doubt play a part, though in varying degree in different cases. In such conditions various degrees of damage up to complete necrosis of liver cells may be present. Necrotic foci in the columns of liver cells may interfere with the passage of bile from the parts beyond, and dislocation, or even swelling, of the liver cells may have a like result. Some cells may contain granules of bile pigment, and the appearance is as if there were an interference with the discharge of bile from these cells ; while in acute yellow atrophy whole areas of parenchyma may be isolated from their bile-ducts. As other possible causes of the jaundice, increased viscosity of the bile and catarrh of the ducts have been put forward.

In many cases of toxic jaundice, e.g. acute yellow atrophy, the serum gives an immediate direct reaction in the van den Bergh test, this pointing to re-absorption of the bilirubin from the liver cells. In other cases, the serum gives the ' biphasic reaction ' (p. 631) ; this might be taken as indicating the presence of both types of bilirubin. There is general agreement that in toxic and infective jaundice, the test is not of much service in differentiating the nature of the condition. Any indication supplied by it is of more value when the test is made on the appearance of the jaundice than at a later period. In cases of toxic jaundice, bile salts are often absent from the urine, the term ' dissociated jaundice ' being then applied ; this, however, is not always the case, especially in the early stages of the jaundice. The symptoms are often of a more severe type than in mechanical or obstructive jaundice, as a result in part of the condition causing the jaundice, and in part of the associated deficiency of the liver, which is often produced by damage to its cells. In some cases the poison present causes also increased hæmolysis, and when this is so the increased formation of bilirubin will tend to accentuate the jaundice.

The relation of toxic jaundice to excessive *hæmolysis* has long been a matter of dispute. The experiments of Minkowski and Naunyn (1886) were for a considerable time accepted as proving that the occurrence of all kinds of jaundice depended on the liver. Using arseniuretted hydrogen as the toxic agent, which causes both hæmolysis and jaundice, they showed that, whereas jaundice was readily produced in normal geese by this substance, it did not occur, or was only slight, when the liver was removed or cut out of the circulation by ligature of its vessels. Thus a jaundice which was considered a typical example of the hæmatogenous variety seemed to depend upon the action of the liver. An entirely new light, however, was thrown on the subject by the work of McNee, who repeated Minkowski and Naunyn's experiments and confirmed generally their results. He found, however, on microscopic examination, that the Kupffer cells of the hepatic capillaries are especially numerous in the goose, and that on poisoning with arseniuretted hydrogen these cells undergo proliferation and become filled with disintegrating remains of red corpuscles, hæmosiderin in various stages of formation and also biliverdin. The non-occurrence of jaundice when the liver is removed is due to removal, not of the liver cells, but of the Kupffer cells which perform the ordinary function of the spleen in other animals, this organ in the goose being of small size. In this way the formation of bilirubin by cells of the reticulo-endothelial system was demonstrated. Subsequent work has shown it to be a fairly common property of cells to split up hæmoglobin into hæmosiderin and an iron-free moiety closely allied to, if not identical with, bilirubin. Even kidney cells, for example, have this property (p. 165).

In order to throw light on bile formation in the healthy animal, the effects of excising the liver or of excluding it from the circulation have been studied. Mann and his co-workers, employing a new method of excising the liver and a very delicate spectrophotometric method for estimating bilirubin, have reached definite results in dogs. They found that formation of bile pigment occurs in the liver but only to a slight extent, most of it being formed extrahepatically. Rather more bilirubin is formed in the spleen than in the liver, but the chief site of extrahepatic formation is the bone-marrow. This result was arrived at by comparing the amount of bilirubin in the blood going to the organ with that in the blood coming from it. It is quite likely, however, that the formation of bilirubin in different sites varies in different animals, and the problem of jaundice is thus rendered more complicated. Further, in Mann's experiments, the bilirubin which appeared after excision of the liver, at first gave an indirect van den Bergh reaction but afterwards sometimes a biphasic one. Accordingly, some bilirubin giving a direct reaction was present, though there seems to be no possibility of its being due to the bilirubin having been acted on by liver cells.

In view, however, of all the recent work it must be regarded as established that the main site of bilirubin formation is an extra-hepatic one and is chiefly in the reticulo-endothelial system, the bilirubin being then excreted by the liver.

(2) **Hæmatogenous Jaundice.** In many cases where excessive hæmolysis is present, there is merely an increase of bilirubin in the blood, as estimated by van den Bergh's method (latent jaundice); but sometimes there is a yellow discoloration of the skin, which may be spoken of as hæmolytic jaundice. This may occur in pernicious anæmia, though the term jaundice was formerly not applied to the condition, and notably in *acholuric jaundice* (p. 465). It is also met with in sickle-cell anæmia and in other rarer types of hæmolytic anæmia. The type of transient jaundice occurring in new-born children, known as *icterus neonatorum*, appears to be of the same variety, and it has been found that at the time of birth the bilirubin content of the serum of normal children is much higher than at a later period. In all these conditions mentioned, there is no evidence of interference with the flow of bile from the liver or of disturbance of the hepatic function, and, as a rule, there is no excretion of bilirubin in the urine. Urobilin is often present in the urine in such cases, and this is discussed below. The bilirubin in the blood gives a negative

direct reaction in the van den Bergh test, or at most a delayed direct reaction of slight degree. In this respect, as well as in its non-excretion by the kidneys, the bilirubin in hæmolytic jaundice differs from that present in ordinary hepatogenous jaundice. When a hæmorrhagic effusion occurs, bilirubin is formed locally from hæmoglobin and is detectable by the van den Bergh test within a few days after the hæmorrhage. The bilirubin always gives an indirect reaction, and this fact accordingly supports the view that in true hæmatogenous jaundice the characters of the bilirubin are due to its not having passed through the liver. The non-appearance of bilirubin in the urine in hæmatogenous jaundice is not due to its small amount, as its concentration in the blood may be higher than the threshold value for the excretion of ordinary bilirubin. It may be noted, however, that in the experiments referred to above, Mann found that the bilirubin which appeared in the blood after excision of the liver, gave at first an indirect and afterwards a biphasic reaction with the van den Bergh test. It is thus clear that the subject requires further elucidation before all the facts can be explained.

Urobilin and Liver Diseases. Reference has been made above to the presence of urobilin in the urine in cases where there is *extensive hæmolysis*, e.g. pernicious anæmia, acholuric jaundice, etc., this being associated with bilirubinæmia and indirect van den Bergh reaction. Urobilinuria is, however, met with in certain *liver diseases* and some further facts may be given with regard to it. The whole subject has been a very controversial one but most of the evidence goes to show that the bilirubin in the bowel is reduced by bacterial action to form stercobilinogen and that most of the latter is excreted in the fæces partly oxidised to stercobilin. Re-absorption of a certain amount of stercobilinogen occurs and this is excreted as urobilinogen, chiefly by the liver but also in small amount by the kidneys. When there is marked excess of bilirubin in the bowel the amount of stercobilinogen absorbed is such that, even when the liver is normal, there is an increased excretion in the urine, partly in the form of urobilin. This is evidently the explanation of the urobilinuria met with in the hæmolytic anæmias. On the other hand, when the amount of stercobilinogen absorbed is normal a damaged liver may be unable to excrete its share and again there is increased excretion in the urine, partly in the form of urobilin. It has been shown by Elman and McMaster that in the dog urobilin disappears from the body when the common bile-duct is ligatured or when the bile is drained off by intubation. Further, damage to the liver by hepatic poisons such as chloroform, phosphorus, etc., which leads to urobilinuria, does not do so when the bile is excluded from the bowel. They found also that obstruction of a bile-duct draining one-third of the liver leads to the appearance of urobilin in the urine; on the other hand, it does not lead to bilirubinuria. Accordingly, it would appear that, provided bile is entering the bowel in a normal way, a liver lesion of moderate degree may lead to urobilinuria. This is in accordance with what has been observed clinically, urobilin being present in the urine in cirrhosis, acute yellow atrophy, cholangitis, abscesses in liver, etc.

Liver Efficiency Tests. The functions of the liver are so manifold, including not only excretion of the constituents of the bile but also the internal metabolism of carbohydrates, fats and proteins, that the information supplied by any one test must necessarily be only of partial nature. The tests most frequently used have been the injections of dyes and certain sugars, lævulose and galactose, though there are others.

The dyes employed are such as are excreted almost exclusively in the bile and the test depends on the rapidity with which they disappear from the blood. Of the dyes, ‘ bromsulphalein ’ (phenoltetrabrom-sulphone-phthalein) is probably the most suitable as it seems to have no toxic action. A given amount is injected intravenously, and then after certain intervals of time the amount in the blood is estimated colorimetrically and compared with that in the case of a normal individual. Delayed excretion may be taken as an indication of impaired liver efficiency, but only in a general way. Kyles, working in my laboratory, has found that in rabbits acute damage to the liver leads to marked interference in the excretion of the dye, but as compensatory hypertrophy occurs in the liver the impairment in the excretion soon passes off. In the case of the sugar tests, the usual method is to administer to the patient in the fasting condition a certain amount of the sugar (e.g. lævulose or galactose) and then estimate the blood sugar at given intervals. In a normal person 50 grm. of lævulose leads to little rise in the blood sugar, but when impairment of liver efficiency is present the blood sugar curve is considerably raised and the elevation is prolonged. Recent opinion is that galactose is the most suitable sugar.

We may say that such tests demonstrate impaired efficiency especially in conditions of general affection of the liver, toxic states, etc. They have been found of value, for example, in estimating the risk of damage to the liver in salvarsan treatment. It must be recognised, however, that when the amount of liver tissue is merely diminished, e.g. in some forms of cirrhosis, extensive metastatic growth, etc., no evidence of this may be supplied by the tests, there being apparently a sufficiency of reserve functional powers. And, when the liver has been damaged its efficiency may be quickly restored by the regenerative and hypertrophic changes which occur.

THE PANCREAS

The dual nature of the pancreas has now been completely established. It is composed of two kinds of tissue with distinct functions—the ordinary acinous or glandular tissue, which produces the digestive secretion of the gland, and the islands of Langerhans, which have been shown to furnish an internal secretion or hormone of prime importance in connection with carbohydrate metabolism. We shall not deal in this chapter, however, with the latter function and the relation of the pancreas to diabetes, as these are more properly considered in connection with the endocrine glands. (Chapter XX.)

Degenerative Changes. Various effects of malnutrition, poisons, etc., are met with in the pancreas as in other organs, but it is unnecessary to do more than mention them. Thus cloudy swelling and even a certain amount of necrotic change occur in infections, fatty degeneration in phosphorus and other poisonings, and sometimes amyloid change from the usual causes. Fatty infiltration or lipomatosis is met with in conditions of obesity, and is often a marked feature when the glandular tissue becomes atrophied, e.g. after obstruction of the duct. Atrophy of the gland is met with chiefly in connection with fibrotic lesions and obstructions of the duct, to be described below; it occurs also in conditions of inanition, and to a certain degree as a senile change. Atrophy of the pancreas without any other change, more properly spoken of as abnormal smallness, has been described in some cases of diabetes in young subjects, but its nature and significance are doubtful. Pigmentation in the form of deposit of granular hæmosiderin, sometimes in great amount, is common in hæmochromatosis (p. 166) and may be attended by diabetes. It is important to note that when the pancreatic tissue is injured in various ways, it is attacked by its own enzymes, and necrosis results. Thus small circumscribed areas of dull yellowish tissue are not uncommon at post-mortem examinations. They are met with especially in conditions of acute and chronic pancreatitis, and obstruction of the ducts with retention of secretion; they are often accompanied by patches of necrosis in the fat around.

Inflammatory Conditions

Acute Pancreatitis. Acute inflammation of the pancreas is usually described as occurring in three main types, viz. *hæmorrhagic*, *gangrenous* and *suppurative* (Fitz). In some cases corresponding in general features to the first type there may be little hæmorrhage, the chief change being necrosis. In fact, one may say that in all types the initial lesion is necrosis of the pancreatic parenchyma.

Hæmorrhagic pancreatitis is a somewhat rare acute affection which occurs most frequently after the age of forty, and it has a distinct association with obesity, also with cholecystitis and gall-stones. It is sometimes spoken of simply as *pancreatic hæmorrhage* or as *hæmorrhagic necrosis* of the pancreas. The disease occurs suddenly with symptoms of abdominal pain, vomiting, etc., and may simulate a case of perforation; in fact, operation has not infrequently been performed on this view. The cause of the rapid collapse and fatal result is not clear; by some it has been ascribed to the pressure by the blood on the semilunar ganglia and cœliac plexus, by others to the absorption from the damaged pancreas of protein derivatives which act as poisons. The latter is probably the correct explanation as the symptoms may occur when there is little hæmorrhage. The peritoneal cavity generally contains a quantity of blood-stained serous fluid, and the presence of numerous patches of *fat necrosis* is a prominent feature. These are specially numerous in the region of the pancreas and in the great omentum, but they occur elsewhere (p. 123). The hæmorrhage into the pancreas and, to a certain extent, into the tissues around, may be so extensive that a dark mass is seen through the peritoneum of the lesser peritoneal sac. The condition of the pancreas, as seen on section, varies somewhat. In some cases it is almost uniformly hæmorrhagic, whilst in others there is a mixture of dull yellowish areas of necrosis with hæmorrhage between and around; and sometimes the lesion is mainly a necrotic one.

On Microscopic Examination, three chief changes are found to be present, viz. hæmorrhage, necrosis, and inflammation; and these are associated in varying proportions. The hæmorrhage may be the outstanding feature, the whole tissue of the gland being infiltrated with blood, whilst somewhat diffuse necrosis of the acini is to be seen at places. Many of the small veins and capillaries are often thrombosed, and this may play a part in causing hæmorrhage. In other cases there are areas of more definite necrosis which affects all the tissues, both glandular and interstitial, and may be accompanied by a considerable amount of leucocytic infiltration (Fig. 402). The inflammatory reaction seems to occur somewhat later, and is most marked in the less acute cases. All the appearances may be interpreted as the result of some toxic agent, which kills the parenchyma and also acts on the vessels, leading to hæmorrhage. Clumps of bacteria, chiefly bacilli, may be present at places, but it is common to find large areas in which none can be found and there is no sufficient evidence for regarding the necrosis as the result of bacterial action.

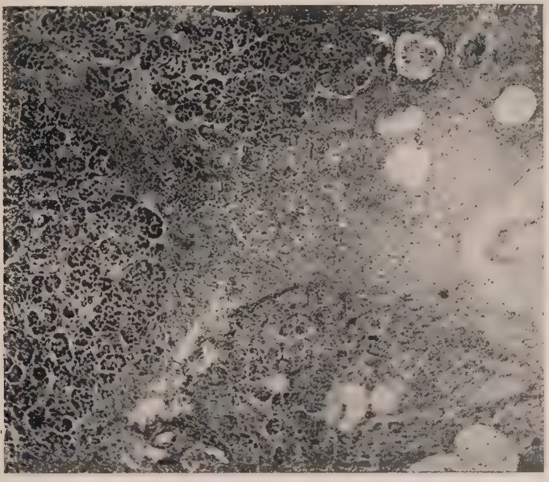

Fig. 402.—Acute Pancreatitis, showing spreading Necrotic Change attended by disappearance of nuclear staining, affecting both Pancreatic Tissue and Fat. × 60

Gangrenous Pancreatitis is generally regarded as merely a late stage of the previous variety. The hæmorrhagic and necrosed tissue becomes secondarily invaded by putrefactive organisms which lead to softening and disintegration of the tissue, so that a large part of the pancreas may become separated and form a sequestrum. These changes are apt to occur when life has been somewhat prolonged. From the infected area, organisms may spread to the peritoneal cavity and cause a local or general peritonitis.

THE ETIOLOGY of hæmorrhagic pancreatitis is, in most instances, obscure. As has been mentioned, it is not infrequently associated with cholelithiasis. In one case of this kind Opie found a small gall-stone obstructing the orifice of Vater's ampulla, and, as the latter was unusually large, the bile had passed along the duct of Wirsung, as was shown by the staining of its lining. This suggested that the lesions in the pancreas might have been produced by the action of the bile, and, on injecting bile into the pancreatic ducts in dogs, he was able to produce hæmorrhage and necrosis in the pancreas. Similar results have been shown to follow the injection of other substances, e.g. dilute hydrochloric acid (Flexner) and also bacteria. It is therefore evident that the pancreatic tissue is very susceptible to the action of irritating substances, but in most cases it is impossible to say what the real cause of pancreatitis has been. We may mention that we have seen a case of acute pancreatic necrosis somewhat similar to Opie's, but in which the obstruction at Vater's papilla was produced by an enterolith which had formed in a duodenal diverticulum closely adjacent to the papilla. The lining of the pancreatic duct was deeply bile-stained and there was no doubt that bile had passed along it. We have also seen bile-staining of the pancreatic duct in pancreatitis without any obstruction.

It has been shown experimentally too that bile can thus enter the pancreatic duct. Archibald injected bile under a certain pressure into the gall-bladder of cats, and found that the resistance at the sphincter of Oddi was sufficient to deviate it into the pancreatic duct and cause necrosis in the pancreas. The application of weak acid to the papilla increased the resistance by causing spasm, but this was not essential for the result. He found that infected bile was more efficient than sterile bile, but attributed this to some change in the bile produced by bacterial action and did not regard the necrosis as the result of infection. Flexner, some years ago, pointed out the importance of the composition of the bile. He showed that the bile salts are specially effective in producing necrosis and that their action is diminished by the presence of protective colloids such as mucin. It may be said that passage of bile, especially when it is infected, into the pancreatic duct is at least a fairly common cause of pancreatic necrosis in the human subject, but this explanation cannot be applied generally. For example, it will not account for the rare cases of pancreatic necrosis where the common bile duct and the pancreatic duct have entered the bowel separately. We may add that experimental work has shown that minor degrees of necrosis may be produced by the methods mentioned and the lesions afterwards may become healed and fibrosed.

Suppurative Pancreatitis is usually caused by extension of organisms along the ducts, but sometimes results by extension from the surrounding tissues. We have seen one case where there was ulceration of a diverticulum in the duodenum, and from this the organisms had spread by the lymphatics to the substance of the pancreas. The suppuration, which is often associated with necrotic change, may occur in one or several foci, and may produce considerable destruction of the gland. Fat necrosis may be present in the tissues around, but it is usually less marked than in the more acute hæmorrhagic lesions.

Chronic Pancreatitis. Though this is fairly common, its etiology is often obscure. The condition would appear, however, to be frequently the result of an ascending infection of the ducts, resulting in catarrh and in injury to the gland parenchyma. Thus it is not infrequently associated with cholelithiasis, and it occurs also when the duct is obstructed, as will be described below. It is believed to be produced by chronic alcoholism, and it is certainly fairly often associated with cirrhosis of the liver. The combination of chronic pancreatitis and cirrhosis of the liver is seen also in hæmochromatosis, where the cirrhotic changes are associated with accumulation of hæmosiderin, the condition known as ‘ bronzed diabetes ’ often resulting. Areas of fibrosis in the pancreas may be produced, as in other organs, by arterio-sclerosis and, as stated above, they may occasionally represent the lesions of mild pancreatitis which have become healed. Lastly, there is a form of diffuse interstitial pancreatitis which is not uncommon in congenital syphilis. The gland is rarely affected in the acquired form of the disease.

In chronic pancreatitis the gland becomes increased in consistence and may be dense and hard. The size varies ; sometimes there may be some enlargement, but more frequently the gland is shrunken, and in a condition of what is called ‘ granular atrophy.’ The histological changes are of the usual type and comprise overgrowth of the connective tissue and atrophy of the glandular elements. The former may be chiefly between the lobules—*interlobular*, or there may be a more diffuse growth between the acini—*intralobular*. In the connective tissue, the small ducts may be unduly prominent, and some of these may be newly formed in the same way as the small bile-ducts in cirrhosis of the liver. The islands of Langerhans suffer less than the glandular acini, but they also may be implicated in the overgrowth of the connective tissue when it is intralobular in distribution, and thus diabetes may result. This is not uncommon in hæmochromatosis. In this condition the evidence is against the view that the deposit of hæmosiderin is the cause of the overgrowth of the connective tissue. We have met with several cases in which the chronic pancreatitis had begun, whilst there was practically no deposit of pigment, although the liver was cirrhotic and extensively pigmented.

Obstruction of Pancreatic Ducts. Obstruction of the main duct may be caused by a pancreatic calculus, occasionally by a gall-stone filling the ampulla of Vater, by a cicatricial contraction, or by pressure of a tumour, most frequently cancer of the head of the gland. When obstruction is produced in any of these ways, the condition of the large ducts varies somewhat, although usually there is some dilatation of an irregular character. The smaller ducts may be similarly affected and may occasionally show cyst-like distension. The result, as in the case of other organs, no doubt varies according as the obstruction is constant or intermittent. In the glandular tissue two changes follow, viz. atrophy of the secreting cells on the one hand, and overgrowth of the connective tissue on the other. In cases of long-standing nature, there are only shrunken remains of the parenchyma to be found in the connective tissue. Sometimes the atrophy is accompanied by a considerable accumulation of adipose tissue. The striking feature, however, is that the islands of Langerhans are not affected by the atrophic process, but, on the contrary, they are more prominent and appear to be more numerous than usual, owing to the shrinking of the other tissues (Fig. 403), and even when the glandular tissue has practically gone, groups of islands practically unchanged remain. Similar results have been obtained by experimental ligation of the pancreatic duct in animals ; here also the persistence of the islands is the outstanding feature. This is of importance in connection with the subject of diabetes, as this condition does not as a rule follow ligature of the main duct.

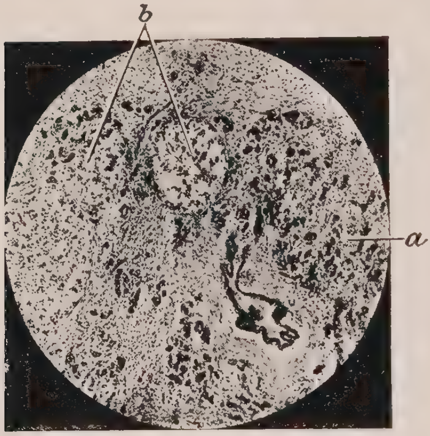

Fig. 403.—Fibrosis of Pancreas secondary to Obstruction of the Duct.

Note marked atrophy of the parenchyma (*a*), while the islands of Langerhans (*b*) are not affected. × 60.

Pancreatic Calculi. These are small concretions composed mainly of calcium carbonate and phosphate, which form in the pancreatic ducts, though their occurrence is rare. As a rule, they are of small size, rarely exceeding that of a pea, and they may be numerous and minute. They are irregularly rounded or elongated in form, of whitish colour and usually of hard consistence. In addition to causing obstruction in varying degree, they may lead to secondary bacterial infection, with acute or chronic inflammatory change as the result.

Cysts. The most important variety is the single ‘ pancreatic cyst ’ which forms a large rounded swelling, sometimes as large as a child’s head. The cyst usually contains a colourless fluid, clear or slightly turbid, though sometimes there may be an admixture of altered blood. The pancreatic enzymes are present in the fluid for a time, and may be detected by the usual tests ; at a later period, however, they disappear. The formation of such a cyst has been observed to occur after injury, and this is regarded as the origin in most instances. The layer of peritoneum over the pancreas is torn and there then occurs an escape of blood and pancreatic secretion into the lesser peritoneal sac, the fluid becoming localised by adhesions. The condition is thus really a *pseudo-cyst* which is situated outside the pancreas. In some cases a similar condition has been ascribed to an attack of pancreatitis with escape of secretion. But it must be admitted that the origin is often obscure. Smaller cysts may be met with in the pancreas from obstruction of ducts, and cysts of congenital origin—the so-called ‘ cystic degeneration ’—have occasionally been observed. A cystic form of adenoma sometimes occurs in the pancreas. Lastly, in Lindau’s disease (p. 789), multiple cysts may occur in the pancreas —‘ cystic pancreas ’—in association with vascular growths in the cerebellum.

Tumours. Apart from carcinoma, tumours of all kinds are very rare in the pancreas. Amongst the simple tumours, fibroma, lipoma, lymphangioma, adenoma and cystadenoma have been described ; the last mentioned may reach a considerable size. Cancer in the great majority of cases occurs in the head, less frequently in the body, whilst cancer in the tail is very rare. The growth is usually of the hard infiltrating variety, though occasionally of more encephaloid type ; as a rule it is an adenocarcinoma, which may mimic the pancrea structure, but sometimes the cells are quite irregularly arranged. The growth in the head practically always leads to obstruction of the main ducts, with exclusion of the pancreatic secretion from the intestine, and usually the common bile-duct also is obstructed. Thus jaundice, clay-coloured stools, interference with digestion, etc., are brought about. The occurrence of sarcoma in the pancreas is quite exceptional.

Recently there have been described a number of cases of tumours of the islands of Langerhans associated with hypoglycæmia. The blood sugar is low, 0·02–0·05 per cent., and there are also definite symptoms ; somnolence, dizziness, loss of consciousness and other nervous symptoms occur from time to time. Death may be preceded by coma. The tumour, ordinarily an adenoma in which the structure of the islets is reproduced, is known as a *nesidiocytoma*—islet tumour. The cells, which are arranged in trabeculæ or irregularly, are both of the A and B type (p. 951), the latter usually preponderating, and they have been found to have a high content of insulin. Areas of hyaline fibrosis may be met with in the tumour tissue and even calcification may occur. Malignancy with metastatic growth has been observed but is a rarity. The administration of glucose leads to amelioration of the symptoms and surgical removal of the growth has led to a cure in quite a number of instances. It is clear that we have here an example of a tumour of an endocrine tissue producing the specific hormone, and in this respect there is a similarity to other endocrine growths, e.g. those of the anterior pituitary lobe, adrenal cortex, etc.

Congenital Abnormalities. Variations in the configuration of the pancreas and in the arrangement of its ducts are not uncommon, but it is unnecessary to describe these in detail. Occasionally the tissue of the head surrounds the adjacent part of the duodenum as a circular band, and a certain amount of stenosis may be produced. This is known as 'ring pancreas.' The occurrence of accessory portions of pancreatic tissue or pancreatic rests is to be noted also. A single rest or several rests may be present, and the commonest site is the submucous tissue of the jejunum, though occasionally they occur in the duodenum and even in the stomach. A pancreatic rest has sometimes been found in the apex of a Meckel's diverticulum and also in an ordinary 'false diverticulum' of the small intestine. In the latter situation it has been supposed that the presence of the rest may cause the diverticulum.

CHAPTER XV

URINARY SYSTEM

THE KIDNEYS

The kidneys are the seat of various lesions corresponding in nature with those of other organs—infective lesions, tumours, etc., but, in addition, owing to their excretory functions, their cells are specially exposed to the action of toxins and poisons of all kinds, and damage produced in this way is very common. Such damage may be recovered from or may lead to permanent disease. In many cases, lesions in the kidney may not lead to any recognisable interference with their function, though the reserve power is probably diminished ; but in others, marked insufficiency is the result, as is shown by changes in the urine and blood, and also by serious symptoms. Such interference with function is specially met with in the various forms of Bright's disease, and furthermore, important secondary effects are produced in other parts of the body. The subject of this affection is one of great clinical and scientific importance and, we may add, of great complexity and demands special consideration.

Atrophy and Hypertrophy

The effects of various conditions which cause atrophy are well illustrated in the case of the kidneys. The commonest cause of nutritional atrophy is interference with the blood supply, and this generally occurs in scattered areas. Thus in arteriosclerosis, the narrowing of the lumen of the minute twigs leads to atrophy of the tissue related, primarily of the glomeruli, and this is accompanied by a varying degree of fibrosis. These changes are of great importance in producing cirrhotic lesions, but they are more conveniently described below (p. 670). When the kidneys become atrophied, there is usually a compensatory increase of the pelvic fat. Functional atrophy is well illustrated when a glomerulus is thrown out of action ; the atrophy then occurs in the system of related tubules. Pressure atrophy is, of course, produced by tumours and other gross lesions. In the general atrophy of the kidney which occurs from dilatation of the pelvis or hydronephrosis (p. 700), various factors are concerned. The accumulation of fluid leads to pressure on, and mechanical stretching of, the kidney substance. The circulation is interfered with and thus nourishment is impaired, whilst at the same time functional activity is stopped. In such conditions great atrophy affects the tubules and then the glomeruli, and there is at the same time overgrowth of fibrous tissue.

Hypertrophy of the compensatory type affecting a whole kidney, is seen when the other kidney is destroyed by such a condition as tubercle, when it is put out of action by the blocking of its ureter, or when it has been excised. In this hypertrophy, there is, of course, no new formation of glomeruli and tubules, simply an enlargement of those existing. The compensatory change varies in degree, being most marked in cases where the lesion has occurred at an early period of life. In cases where one kidney is congenitally absent—*agenesia* (a rare condition), or congenitally small—*hypoplasia*, the vicarious hypertrophy may be practically complete. *Local hypertrophy* of the compensatory type is often seen in the surviving tissue in the neighbourhood where there has been extreme damage or destruction in chronic nephritis. Such a change reaches its highest development, affecting both glomeruli and tubules, where the vascular supply to these is unimpaired, as may be seen in chronic pyelonephritis in early life. This 'focal hypertrophy,' which needs for its occurrence a comparatively healthy condition of the cells concerned, is comparable with the hypertrophic change seen in the liver in cirrhosis.

CIRCULATORY DISTURBANCES

Chronic Venous Congestion. In general passive hyperæmia due to cardiac or pulmonary disease, the kidneys come to show characteristic changes. In addition to being markedly congested and of dark colour especially in the medullary portions, which have a deep purple appearance (Fig. 404), the organs are markedly firmer and more elastic than normally—*cyanotic induration*; and the weight is slightly increased. The increase in consistence is due

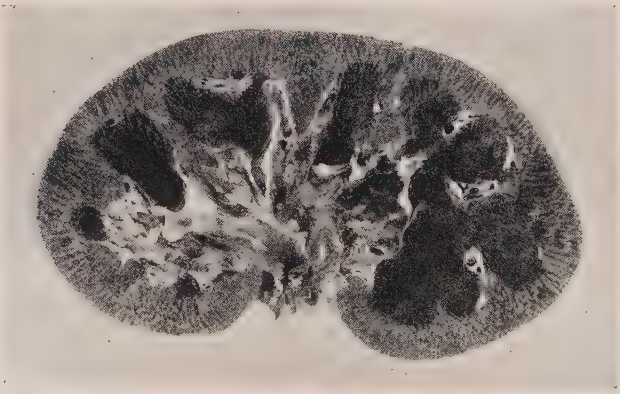

Fig. 404.—Kidney in Chronic Venous Congestion, showing the characteristic appearance due to intense vascular engorgement. × $\frac{3}{4}$.

mainly to a general thickening of the capillaries of the organ, but little or no new formation of connective tissue is to be found on microscopic examination. As a rule, in chronic venous congestion the capsule of the organ strips readily and leaves a smooth surface, but sometimes slight irregular granularity is present and this may be distinct. Some writers consider that a form of irregular fibrotic kidney may be produced by passive hyperæmia, but it seems to us that where there is distinct fibrosis it is due to some cause other than the congestion. In cases where passive hyperæmia of the kidneys is marked, the urine is usually decreased in quantity and concentrated owing to the deficient circulation through the organ, and it often contains a certain amount of albumin and, it may be, a few red blood corpuscles.

Acute Congestion occurs in connection with various inflammatory lesions, especially when they are of focal character, but it needs no separate description.

Obstruction of Vessels. Infarcts as the result of closure of arterial branches, and their characters, have already been described (p. 27). They are usually the result of embolism, especially in cardiac cases, but they may be produced also by local thrombosis in diseased arteries. The occurrence of an infarction is generally associated with the presence of a varying amount of blood in the urine. Infarcts are met with in various stages of absorption and shrinkage, and their former presence may be indicated merely by cicatricial depressions ; sometimes these are numerous and produce an irregularly nodulated kidney. In cases of puerperal eclampsia distinct necrotic areas are sometimes present, and in a few cases recorded nearly the whole organ has been the seat of infarction. The latter occurrence, which is illustrated in Fig. 420, is referred to below. Septic infarction and abscess formation are described below (p. 688).

Sudden blocking of the renal vein leads to diffuse hæmorrhage and to swelling of the kidney; there may be considerable necrosis throughout the organ. If, however, the obstruction is gradual, little or no change may result, owing to the development of anastomosis with collateral veins.

DEGENERATIONS AND INFILTRATIONS.

Cloudy Swelling. This is of frequent occurrence in the kidneys in septic and infective conditions. It is met with also in various poisonings, e.g. by carbolic acid, corrosive sublimate, etc. As we have said, it is the earliest indication of damage done to the cells, and intermediate stages to actual necrosis are often to be found ; it may be followed also by general fatty degeneration, as is not uncommon in cases of septicæmia. When the kidneys are the seat of cloudy swelling they become somewhat swollen and tense. The consistence is diminished so that the cut surface bulges somewhat, and the cortex is of pale pinkish colour and often of blurred appearance. It is, however, not possible from the naked-eye examination to judge definitely of the degree of damage present. There is no evidence that cloudy swelling, as ordinarily understood, is produced by any distinct functional disturbance. In cases of poisoning, however, e.g. with corrosive sublimate, further damage may lead to urea retention. As has been previously stated, the appearances of cloudy swelling readily become accentuated by post-mortem autolytic change.

Fatty Degeneration. Two distinct forms of this condition are to be recognised, (*a*) a diffuse or regular and (*b*) a patchy or irregular. The former, in which there is practically uniform affection of the kidney substance, is met with in the general conditions which lead to fatty degeneration—in anæmias, especially pernicious anæmia, in various septic and toxic conditions and fevers, as a sequel to cloudy swelling, and in various poisonings such as phosphorus, chloroform, etc. Fatty degeneration is sometimes marked in cases of diabetes, notably where there has been coma ; also in some cases of hyperthyroidism. Its occurrence is shown by the cortex becoming paler, of yellowish tint which may be slight or well marked, and of duller aspect ; the minor degrees of the condition, however, can be detected only on microscopic examination. The fat in the form of minute globules is present chiefly in the convoluted tubules and the ascending limbs of Henle's tubules, but in marked cases it may be more widespread. It may be noted that extreme fatty degeneration may occur, e.g. in pernicious anæmia, without any disturbance of function.

The patchy or irregular type of fatty degeneration occurs in kidneys already the seat of other lesions, especially nephritis and amyloid disease. In the former, there is fatty change in the cells of the tubules and some may be filled with collections of desquamated and fatty cells. As the change takes place in an irregular manner, the cortex of the organ comes to show a yellowish mottling or speckling. In cirrhotic kidneys, it is common to find fat in the walls of the small arteries. The fat in these conditions mainly consists of the ordinary glycerol esters, but often a certain amount of doubly refracting fat (cholesterol esters) may be present. The latter occurs in the tubules and glomeruli, but accumulates also in the interstitial tissue and sometimes comes to form numerous large collections in that position. The term 'myelin kidney' is then applied, and the condition can often be recognised by the fact that the yellowish areas are duller and more granular in appearance, and more sharply marked off from the surrounding tissue than in the ordinary form of fatty degeneration. In such cases globules of doubly refracting fat may be present in the urine. Accumulation of cholesterol fat in the tubules, etc., is a prominent feature in nephrosis (p. 661) and is associated with hypercholesterolæmia, to which it is evidently due.

Amyloid Degeneration is described below (p. 686).

Deposits of Pigment, etc. The chief forms of pigment proper met with in the kidney are blood pigment and bile pigment.

(A) *Blood Pigment.* When there is marked hæmoglobinuria or methæmoglobinuria, the hæmoglobin which is excreted by the glomeruli gradually becomes concentrated on passing down the tubules, and not infrequently forms granular masses or hyaline cylinders in the lower parts ; the kidney comes to have a brownish colour, which in the medulla has a streaked appearance. This occurs, for example, in paroxysmal hæmoglobinuria, blackwater fever, sometimes in severe burns, poisoning with chlorate of potash, etc. ; it is also met with after transfusion with incompatible blood. When the hæmoglobinuria is repeated as in the paroxysmal form, there may be a considerable accumulation of hæmosiderin in the cells of the convoluted tubules. In pernicious anæmia also, hæmosiderin is often present in the cells of the convoluted tubules (p. 456). The earliest indication of the presence of hæmosiderin is a diffuse iron reaction, given first by the cells in the upper parts of the convoluted tubules, which seem to have the faculty of being able to break up the hæmoglobin re-absorbed from the glomerular filtrate, retaining the iron-containing moiety.

(B) *Bile Pigment.* In cases of jaundice the kidneys are bile-stained in common with other tissues, but the colour in them becomes more marked owing to the fact that the pigment is in process of excretion and in chronic cases is deposited in solid form. In the jaundice met with sometimes in children at the time of birth—*icterus neonatorum*—the pigment occurs in the form of fine needles and rhombic crystals of hæmatoidin, and the deposit is at the apices of the pyramids, within the tubules and in the interstitial tissue ; the term *bilirubin infarct* is often applied. In the adult, in cases of chronic jaundice, fine granules of pigment may be seen in the cells of the convoluted tubules and in material separated from them, whilst in the lower tubules, apparently by concentration, denser and sometimes hyaline fragments of olive-green colour are present.

Among other substances deposited, *lime salts* and *urates* may be mentioned. With regard to the former, calcification occasionally occurs in the damaged cells or their remains in the tubules in nephritis, but only to a slight extent. In cases of corrosive sublimate poison, however, where the patient has survived for some time, there is usually extensive calcification of the tubules ; it can be produced readily in rabbits by poisoning with this substance. The incidence of the calcification is supposed to be due to interference with the normal excretion of lime salts by the intestine as the result of damage done. Occasionally, especially in old people, lime salts in amorphous form are deposited in the interstitial tissue at the apices of the pyramids—'lime infarcts' ; calcification may be met with in the blood vessels. In osteomalacia and in osteitis fibrosa, metastatic calcification occasionally supervenes, and the deposit is more widespread, affecting interstitial tissue, blood vessels, and even glomeruli and tubules.

Metastatic calcification in the kidneys may be produced experimentally in animals by the administration of large doses of vitamin D in the form of irradiated ergosterol, and also by parathyroid extract (parathormone) (pp. 828, 954).

Deposits of *urates* occur in two conditions. In new-born children they are commonly to be found as brownish-yellow streaked deposits at the apices of the pyramids, called *uric acid infarcts*; and they are due to an accumulation of urates, chiefly of urate of ammonia in the form of minute spheres, within the collecting tubules. As a rule, they soon disappear, but they may occasionally be found at a later period and calculi may originate in connection with them. The second form of deposit is met with in granular kidneys, especially in gout, though also in other conditions. The deposit of urates is indicated by the presence of lines of pale brownish tint and of dull lime-like appearance, in the medulla and especially towards the apices of the pyramids; these are due to collections of sodium biurate in the form of needle-like crystals, as is seen in the lesions of gout. The deposit is mainly in the interstitial tissue and may be associated, as elsewhere, with a certain amount of necrotic change. At the margin, there may be formation of giant-cells.

BRIGHT'S DISEASE—NEPHRITIS

The essential fact established by Richard Bright in his remarkable book published in 1827[1] is that certain conditions of disease characterised by albuminuria and often attended by œdema are due to structural changes in the kidneys. He described and illustrated these changes at different stages and in some cases traced their origin. It is specially interesting to note that he recognised that a late stage of the diseased condition might originate from scarlet fever. In the want of knowledge as to the microscopic changes in the lesions described by him, it is not possible to give a satisfactory definition of Bright's disease, but it is customary to use the term in a general way and to include conditions which may be reasonably supposed to be of the same nature as, or closely related to, those described by him. The term nephritis is more definite but not sufficiently comprehensive, though it is used as synonymous by some writers.

Whilst the histological changes in the various forms of nephritis have been worked out with tolerable completeness, their etiology is far from being properly understood. In certain conditions the kidneys are invaded by organisms, and inflammatory or suppurative lesions result; but in the ordinary forms of nephritis as usually understood, there is no evidence that the lesions are due to the actual presence of organisms, though they are in some way caused by their toxins or other chemical substances. The suppurative lesions will be considered under a separate heading, as will also be the subject of amyloid disease.

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[1] See *Original Papers by Richard Bright on Renal Disease*. London, 1937.

The lesions of the kidneys in nephritis are ordinarily classified as *acute*, *subacute*, and *chronic*. The arrangement is convenient, though of course all intermediate stages are met with, and acute changes may be added to those of a chronic nature. These varieties correspond in a general way both with naked-eye appearances and minute changes. Thus *acute* nephritis is characterised chiefly by effects on the capillaries, exudation, leucocytic emigration, etc., and by degenerative changes in the tubules; and the kidneys are swollen or moderately enlarged. In *subacute* nephritis the outstanding changes are proliferative in nature, and the kidneys undergo considerable enlargement; whilst in *chronic* nephritis the fibrous contraction and atrophy are the outstanding features and the kidneys usually become shrunken in varying degree. Such a description is to be accepted only as a general guide, for example, markedly chronic changes may abound while the organs are still enlarged or are of normal size.

Nephritis, starting as an acute affection, may pass through all three stages mentioned, and the kidneys ultimately become shrunken and granular. Such an event is well seen in cases of nephritis following scarlet fever in young subjects. It may be noted that sometimes clinical evidence of an acute attack may be wanting, and the lesions found at the post-mortem examination may be in the subacute or chronic stage. Here, either the disease has started as a subacute affection, or any acute stage has been little marked.

There is, however, a very important group of cases where the kidney damage is not caused by acute or subacute inflammation but is due to arterial disease. The changes are the result of interference with the blood supply, are insidious and slow in their progress; we may say of chronic nature from the outset. Fibrosis and atrophy are outstanding results and these vary greatly in their distribution and extent. The term nephrosclerosis or primary renal fibrosis will be used to include all such effects.

CLASSIFICATION.[1]—The lesions in Bright's disease are very varied in type and many classifications have been put forward. The following short outline is mainly according to the structures first or principally affected, through the clinical bearings also are taken into consideration.

(A) *Glomerulo-nephritis.* We use this term as it indicates the *primary site* of the lesion. The other structures of the kidney, tubules, interstitial tissue and blood vessels, soon become secondarily involved. The great majority of cases of nephritis are of this nature. In its chief form it is a diffuse affection of the glomeruli. Glomerulo-nephritis is met with in acute, subacute and chronic stages.

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[1] For details on this subject, see *A Classification of Bright's Disease*, by Dorothy Russell, Medical Research Council, London, 1929; *Recent Advances in Pathology*, by G. Hadfield and L. P. Garrod, 3rd edit., London, 1938; and *A Study of Nephritis and Allied Lesions*, by J. Gray, Medical Research Council, London, 1933.

In one form of glomerulo-nephritis called 'embolic nephritis' bacteria are actually present in the capillaries of the glomeruli. This form will be considered by itself (p. 668).

(B) *Tubular or Degenerative Nephritis.* In this variety there is acute tubular damage produced by toxins or by chemical substances of known constitution.

(C) *Lesions due to Arterial Disease.* These form a definite group by themselves and are considered together under the heading *nephrosclerosis* or *primary renal fibrosis*, the term 'primary' being used in the sense of not secondary to inflammatory change. There are two chief varieties, (*a*) the more important is associated with hypertension, we may call it *hypertensive nephrosclerosis*, (*b*) the other occurs in old age without hypertension—*senile nephrosclerosis.*

In writing the following account I have been much indebted to the writings of Professor Shaw Dunn, whose work, both observational and experimental, has thrown light on many important points.

GLOMERULO-NEPHRITIS

Acute Glomerulo-Nephritis. This occurs most frequently as the result of infection with hæmolytic streptococci. It occurs not infrequently as a sequel to scarlet fever, usually about the third week and often after the temperature has fallen. The primary focus is usually sore throat or tonsillitis, but it may be in the middle ear, in wounds, etc., or acute rheumatism. It occasionally follows diphtheria and influenza, but here again streptococci may be concerned. Sometimes, though much more rarely, there is a relation to pneumococcal infection. Chill may be a determining factor. In the conditions mentioned, the lesion is in some way to be regarded as of toxic origin, there being no evidence that organisms are actually present in the kidneys. It, however, does not depend on the severity of infection and amount of toxin formation; in fact, it often develops in quite mild cases. Another point is that usually some time elapses between the onset of the infection and the nephritis. Further, it is not possible to produce the typical glomerular lesions merely by the injection of streptococcal toxin. These facts have led some observers to put forward the view that the affection of the glomeruli is really an example of allergy; the tissues are first sensitised by a small amount of toxin and then further access of toxin produces the lesions. It is, however, not possible to speak definitely on this point.

Glomerulo-nephritis was the primary lesion in 'trench nephritis' or 'war nephritis,' which affected considerable numbers of the troops in the war (1914–18). The exact etiology of war nephritis was not determined, but it was shown that the affection could not be ascribed to exposure, to unsuitable diet or water supply, or to any of the recognised infections. It may have been due to a filter-passing virus but for this no clear evidence was obtained.

In connection with the pathology of acute glomerulo-nephritis, it is important to note that the immediate mortality is low. In some cases the disease leads subsequently to serious permanent lesions, whilst in others it apparently returns to a normal state and there is no recurrence; in the latter the lesions may be supposed to be of mild order. These facts were strikingly exemplified in the case of war nephritis.

Many attempts have been made in the past to reproduce experimentally the features of glomerulo-nephritis in animals, but as a rule without success. Recently, however, acute and subacute nephritis with damage to the glomerular capillaries have been found to result from the injection of autolysates of streptococci and pneumococci (Rich, Blackman and others). Another important method of producing glomerular nephritis experimentally is by the use of antisera (Matsumi). The serum is prepared by repeated injections of emulsions of rabbits' kidneys, freed from blood, into ducks. The serum of the duck acquires nephrotoxic properties and when injected into rabbits, leads to glomerular changes closely similar to those in the human disease. The method promises to be of much use in studying the effects of the glomerular lesions.

To the naked eye, the kidneys in glomerulo-nephritis usually show some degree of swelling; the capsule may be tense and on its being stripped minute hæmorrhages may be seen. The cortex is pale, sometimes broadened and contrasts with the medullary pyramids which are congested. The normal markings are faint owing to pallor or they may be blurred owing to patchy congestion. The tissue may be somewhat œdematous. On the other hand, the kidneys may appear comparatively normal. On examination of the cortex, however, with a hand lens, the Malpighian bodies may generally be seen to be enlarged, and to project as small translucent structures from the cut surface; as a rule they contain little blood and are paler than the general parenchyma.

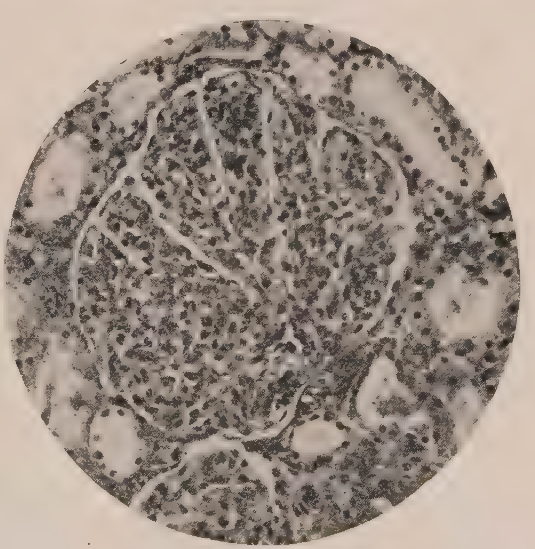

Fig. 405.—Malpighian Body in Acute Glomerulo-Nephritis, showing increased cellularity and lobulation of glomerular tuft. Note irregular outline of the latter. × 200.

On Microscopic Examination the glomeruli generally are large and fill their capsules, and there is distinct increase of nuclei in them (Fig. 405). Many may have lost their circular form (Fig. 406), owing to unequal swelling, and sometimes a portion of a tuft is seen projecting into the first part of the tubule. The richness in nuclei is due chiefly to increase of the endothelial cells of the capillaries but partly to leucocytic infiltration. The endothelial cells become swollen, proliferate, and may form syncytium-like masses; thus the lumina of the capillaries appear narrowed or obliterated and most of them are empty of blood. This, however, does not imply that the capillaries are impervious to blood. At a very early stage they may be actually congested. Polymorpho-nuclear leucocytes are present in the tufts, and they may accumulate in the interstitial tissue around the glomerular arterioles. In some cases the epithelium lining the capsules of Bowman shows little or no change, but in others it is markedly affected. It undergoes proliferation and there results a crescentic mass of somewhat spindle-shaped cells underneath the capsule (Fig. 407). This, when it occurs, is a somewhat later change but may be seen as early as the third week. The number of glomeruli which show 'crescents' varies much in different cases. Their occurrence is associated with other signs of severe damage. Some of the glomerular capillaries may be thrombosed, and there may be albuminous or fibrinous exudate, red corpuscles and leucocytes within the capsules of Bowman. In view of these changes many distinguish (*a*) an intra-

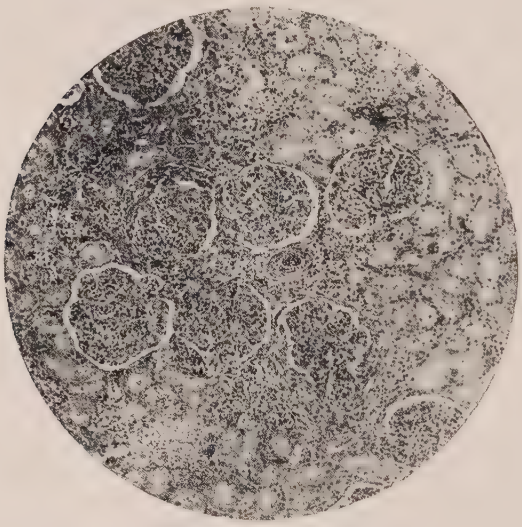

Fig. 406.—Acute Glomerulo-Nephritis, showing the swelling and increased cellularity of the Glomeruli, also their irregular form. × 60.

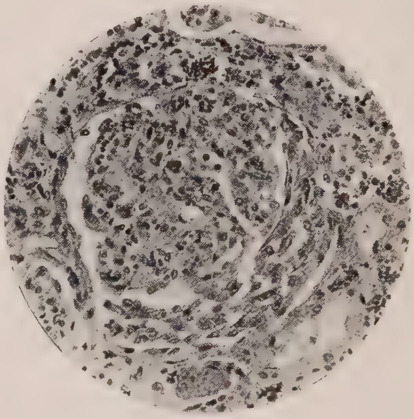

Fig. 407.—Malpighian Body in Acute Glomerulo-Nephritis, showing the proliferation of Epithelium within the capsule of Bowman. × 200.

capillary type and (*b*) an extracapillary type ; the latter, in which the capsular changes occur, is a more severe condition. The distinction is of importance in connection with the changes which may follow.

In the *tubules*, at an early date, little alteration may be present. The cells, especially of the convoluted tubules, may be swollen, foamy or granular, and some disintegration of their extremities may be present. A few mitotic figures may sometimes be seen. Fine fatty droplets may appear in the cells and another change which often develops is the appearance of hyaline droplets. Small droplets appear in the cytoplasm of the excreting cells and these can be stained by Gram's method. They are of protein nature and probably represent the result of absorption of proteins from the contents of the tubules. Catarrhal desquamation of epithelial cells also may occur and this may be followed by reparative change. When such tubular changes have developed the condition may be spoken of as a *glomerulo-tubular nephritis*. The point to be noted, however, is that the primary and important damage is in the glomeruli.

Functional Effects. The changes described in the glomeruli interfere with the circulation through them and are thus concerned in the diminution in the amount of urine which results ; sometimes there is actual suppression. Albuminuria, hæmaturia, also casts of various kinds, are present in varying degree. A certain amount of general œdema is often present, and all the excretory functions of the kidneys may be interfered with. Not only may there be retention of salt and water but also of urea, owing to failure of the tubules to concentrate it. There is often some rise of blood pressure and there are sometimes also convulsive seizures with occasionally a fatal result. The significance of the functional effects are considered more fully later. While complete recovery from the clinical point of view often occurs, there is probably always some permanent damage to some of the glomeruli ; not infrequently the glomerulitis passes into a subacute stage and leads to serious results. This will be the case especially when subcapsular epithelial proliferation has occurred.

Subacute and Chronic Glomerulo-Nephritis. The affection is the result of a previous acute glomerulo-nephritis, and its etiology is the same. In some instances no history of an acute attack can be obtained, and in these the disease either has started as a subacute affection or, as is more likely, the acute stage has been of slight degree. Though a subacute stage of enlargement and a chronic stage of contraction are ordinarily distinguished, these are to be taken merely as types ; all transitions in the evolution of the disease are met with.

The subacute stage is characterised by proliferative changes in Malpighian bodies, interstitial tissue and tubules, and by the accumulation of fatty and lipoid material in the last. The kidneys are enlarged, each sometimes weighing eight ounces or more. The capsule usually strips easily and leaves a smooth surface, though slight adhesions may be present. The surface is pale on the whole, and has a greyish-white colour on which the venæ stellatæ stand out distinctly; the vessels are irregularly congested and minute hæmorrhages are not uncommon (Fig. 408). On section, the cortex, both superficial and inter-pyramidal, is increased; it is pale and mottled with yellowish specks, due to fatty change in the tubules. Occasionally much lipoid is present and then the yellow marking is more distinct; the term 'myelin kidney' is then applied. On the other hand when the changes are chiefly glomerular and interstitial, there is little mottling and the consistence of the kidney tissue is firmer. The parallel markings in the cortex are usually fairly regular but the vessels are unequally filled with blood. The medulla also is paler than the normal. Occasionally a hæmorrhagic condition is superadded, and then the cortex is studded with petechiæ, while the medulla may have a dark red colour (Fig. 412).

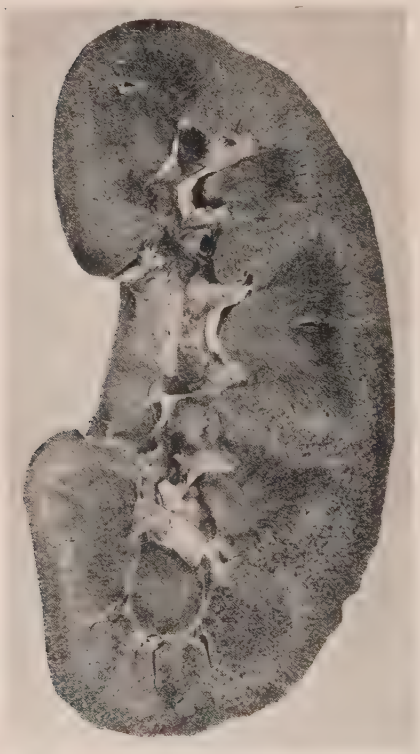

FIG. 408.—Enlarged Kidney in Subacute Nephritis.

The parenchyma is less pale than usual owing to minute hæmorrhages. (Compare with Figs. 416, 417.) × $\frac{3}{4}$.

On MICROSCOPIC EXAMINATION, the Malpighian bodies present various changes. Most are enlarged and the glomerular tufts are rich in nuclei, owing to proliferation both of endothelial and connective tissue cells; many of the glomeruli have a lobulated form. In one type, the extracapillary or capsular, proliferation of the sub-capsular epithelium is still a marked feature, and there thus result several layers of cells forming a crescentic mass under the capsule. Connective tissue fibres have appeared in the cell masses, and fibrous laminæ are thus formed in the site of the space. In other instances there may be concentric growth of connective tissue around the capsule (Figs. 409, 410); this is seen especially when general increase of the connective tissue of the organ is a marked feature. Another important lesion often seen is adhesion between the glomerulus and the capsule, by which the space becomes obliterated. Some of the glomeruli may be shrunken and fibrous owing to narrowing of the afferent arteriole by

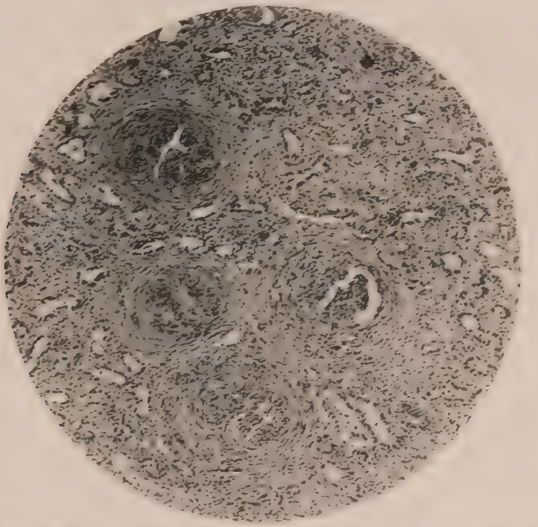

FIG. 409.—Subacute Glomerulo-tubular Nephritis of Extracapillary Type, showing proliferative changes in and around the Glomeruli and also increase of the Connective Tissue. × 60.

endarteritis. In fact we have the picture of a progressive affection in which more and more of the glomeruli are thrown out of action. In the neighbourhood of glomeruli showing capsulitis there is usually considerable overgrowth of connective tissue.

In a second type there is no capsulitis, but we see a later stage of intracapillary glomerulitis. The glomeruli are still enlarged but are less cellular owing to fibrous change between and also within the capillaries (Fig. 413). A later change of actual sclerosis may be present in some. The result of the glomerular lesions will be an increasing interference with the blood flow.

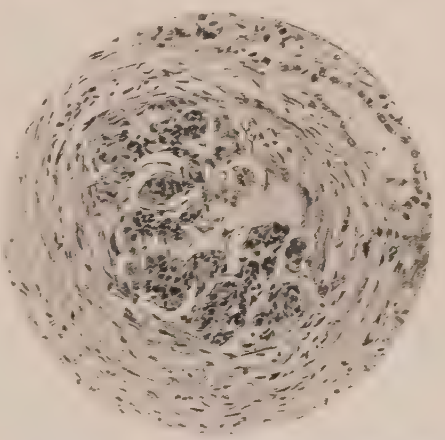

FIG. 410.—Malpighian body in Subacute Nephritis, showing Proliferation within the Glomerular Tuft and also around. × 200.

The changes in the tubules in association with these glomerular lesions are also markedly various. Some are atrophied whilst others are rather dilated and lined by a low regenerated epithelium. Again, there may be marked accumulation of fatty and lipoid material in the cells, also hyaline droplet change; catarrhal proliferation may be a feature in some cases. These different changes are associated with interstitial overgrowth of connective tissue; this may be in fine bands and fairly general, or more extensive in certain areas, especially in relation to capsulitis. Arterial changes vary much in degree but there is often intimal thickening.

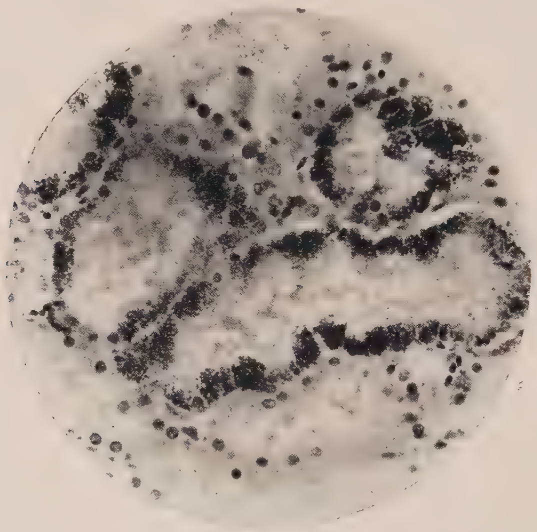

FIG. 411.—Hyaline Droplet Change in Convoluted Tubules in Subacute Nephritis. (J. S. D.) × 250.

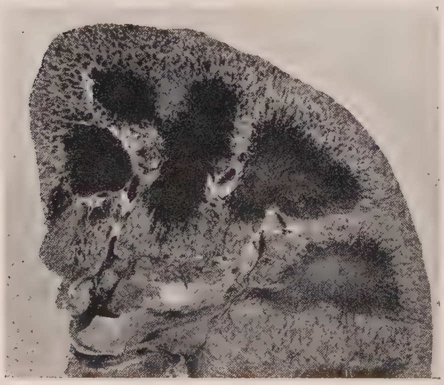

FIG. 412.—Portion of Kidney, showing Hæmorrhagic Nephritis. The condition had become superadded to subacute nephritis. × $\frac{4}{5}$.

Lipoid Nephrosis. In a few cases the glomeruli are very slightly affected or may appear normal. In the tubules the outstanding feature is the marked accumulation in the epithelium of fatty material, especially of lipoid nature (Fig. 414). A considerable amount of such material may accumulate in the interstitial tissue. There is practically no catarrh and no increase of interstitial tissue. Such a condition was called by many *lipoid nephrosis,* and it was supposed to be distinct from glomerulonephritis. It is now coming to be recognised that it is a form of the latter in which the glomeruli have been only slightly damaged.

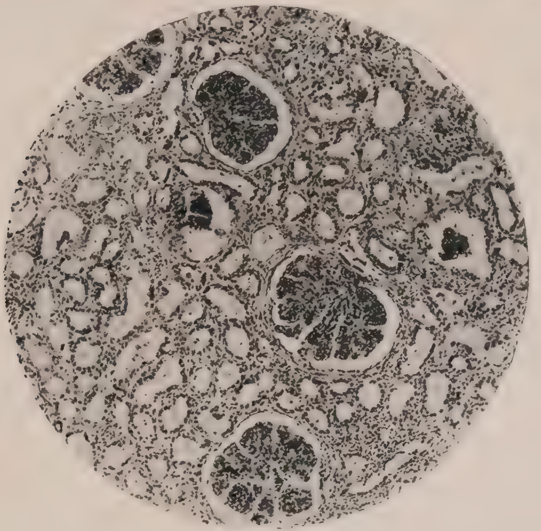

FIG. 413.—Subacute Nephritis of Intraglomerular Type.

Note large digitate glomeruli with early fibrous increase, tubules with low epithelium and diffuse increase of interstitial tissue. (J. S. D.) × 60.

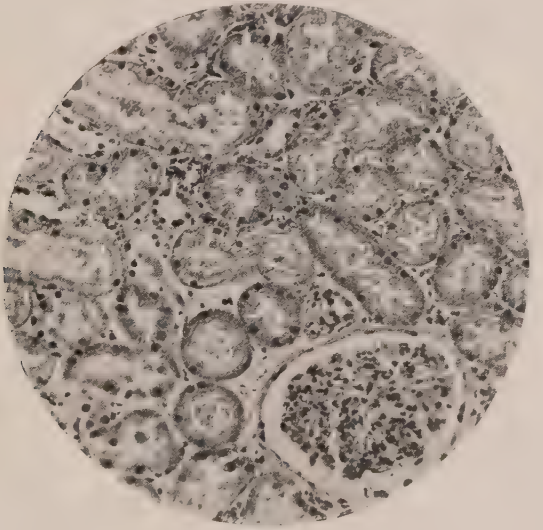

FIG. 414.—Kidney in Nephrosis, showing fatty accumulations in excreting tubules.

Note absence of glomerular and interstitial change.

Slight evidence of previous inflammatory change such as swelling of the basement membrane of the capsule or some capsular lesions may be seen, but the most important abnormality is that described by Shaw Dunn. This consists in a general patency of the glomerular capillaries, these appearing circular on section and showing hyaline thickening of the capillary basement membrane (Fig. 415). The significance of this will be presently described.

Functional Effects. In acute glomerulonephritis, as has been stated, all the functions of the kidney may be impaired but if the disease progresses the disturbances usually become arranged as two main types. One is characterised by urea retention and raised blood pressure, with resulting arterial and cardiac changes and by the absence of œdema. It is commonly called the *azotæmic* type. In the other the chief features are retention of salt and water, with œdema, and the absence of urea retention and cardio-vascular changes. It is known as the *nephrotic* or *hydræmic* type, and it is not uncommon for it to occur without a definite history of acute attack. It must be noted, however, that in some cases of this type there is later a change of features into those of the azotæmic type.

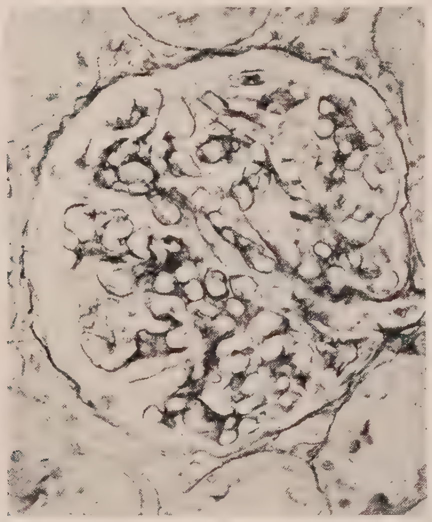

Fig. 415.—Malpighian body in Nephrosis, showing patency of Capillaries with some Hyaline thickening of Walls. Mallory's stain. (J. S. D.) × 300.

The azotæmic type develops a varying period after acute glomerulonephritis. There is albuminuria, but this tends to diminish as the disease goes on and may practically disappear as the last stage is reached. Red corpuscles, leucocytes and casts—granular, hyaline and epithelial—are to be found in the urine in varying numbers. But as has been stated, the most important features are urea retention and hypertension; the blood urea may rise to 150 mg. per 100 c.c. or higher, while the heart becomes distinctly hypertrophied. Unless death occurs from uræmia or other cause at this stage, the case gradually assumes the characters of a chronic nephritis.

The features of the hydræmic type form a fairly definite group—the ' nephrotic syndrome '—and Shaw Dunn has given an explanation of their occurrence taking the hypercholesterolæmia, which is present, and increased permeability of the glomerular capillaries as a basis.

The increased permeability may be the result of glomerulonephritis when it is present or of the dilated state of the glomeruler capillaries, when definite evidence of inflammatory change is absent. (Krogh showed that the normal impermeability of most capillaries to protein becomes lost to some degree when they are dilated.) The permeability cannot, however, be much increased as there is little or no escape of red corpuscles. The glomerular filtrate will thus contain a small amount of protein, some of which is absorbed and appears as hyaline droplets in the epithelium, but most passes in the urine. Owing, however, to the great concentration which the filtrate undergoes in passing along the tubules (about 100 times) it is evident that a small quantity of protein in the original filtrate may give rise to an abundant albuminuria. The glomerular filtrate owing to the state of the blood will also contain lipoid and fatty substances in excess. These are absorbed by the tubules and give rise to the characteristic changes described. In these ways the main features may be satisfactorily accounted for. The very important association of oliguria with absence of urea retention is most satisfactorily discussed at a later stage. A similar syndrome is present in amyloid disease—‘amyloid nephrosis.’

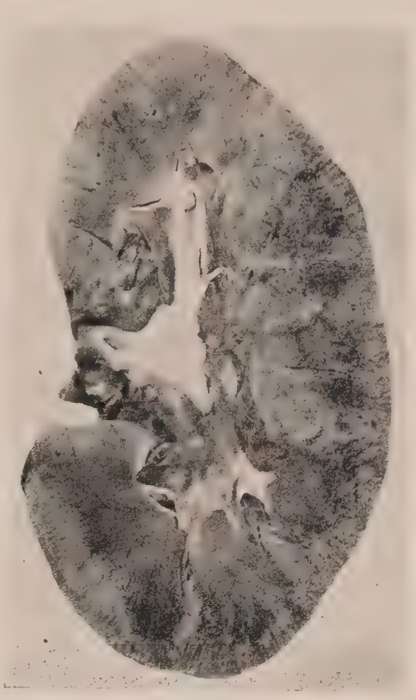

FIG. 416.—Subacute Nephritis in early stage of contraction; the cortex is becoming thinned and shows irregular mottling. $\frac{3}{4}$.

CHRONIC GLOMERULO-NEPHRITIS. The chronic stage is characterised by the contraction of the fibrous tissue formed in excess, though there is no definite line between it and the subacute. In cases where the lesion has been *diffuse* a general shrinking of the cortex with some fine granularity is present, but death usually occurs before the change has progressed farther. On the other hand when the acute glomerulonephritis has been uneven in its distribution, so that some glomeruli have escaped or been able to recover, life may be prolonged and marked irregular shrinking of the organ occurs. The result is the *small granular kidney* of chronic glomerulonephritis, also known as the secondarily contracted kidney.

The passage of subacute nephritis into the chronic contracted stage is evidenced by the surface of the kidneys becoming uneven. The superficial cortex becomes progressively thinned and its markings irregular, while the inter-pyramidal cortex remains for a time less affected (Fig. 416). Ultimately a stage may be reached in which the organ is shrunken and granular on the surface, and the cortex is reduced to a mere rind, which has entirely lost its normal parallel markings and shows pallor often with yellowish mottling (Fig. 417). The consistence is firm and the capsule is usually very adherent. The size of the kidneys may be greatly reduced; in fact, some of the smallest specimens of granular kidney are of this type. During the stages of contraction the pale appearance is usually maintained and the kidney in the final stage is sometimes called the 'pale contracted kidney.' The shrunken kidneys may, however, sometimes be red, as in the primary type (p. 672).

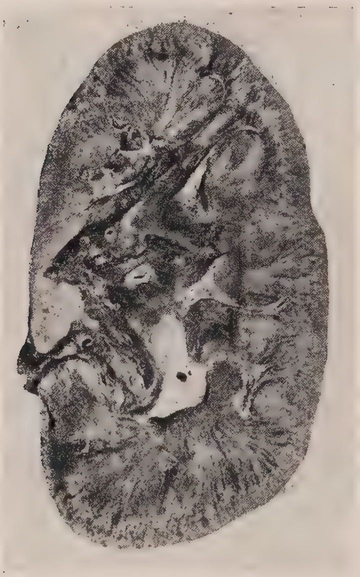

FIG. 417.—Chronic Nephritis in stage of contraction—granular Kidney of secondary type. $\frac{3}{4}$.

On MICROSCOPIC EXAMINATION, we see a continuation of the changes described in the subacute stage. The depressions in the cortex correspond with areas of overgrowth of connective tissue. Many of the glomeruli are fibrosed (Fig. 418), although others still show the intracapillary and extracapillary proliferative changes described. The connective tissue occurs chiefly along the intralobular vessels, and in it the glomeruli are irregularly arranged; some of them are scarcely recognisable and are evidently in process of disappearance. In other parts glomeruli which have escaped damage may show relatively little change. Many of the tubules, having had their function cut off by throwing out of the glomeruli, are atrophied and

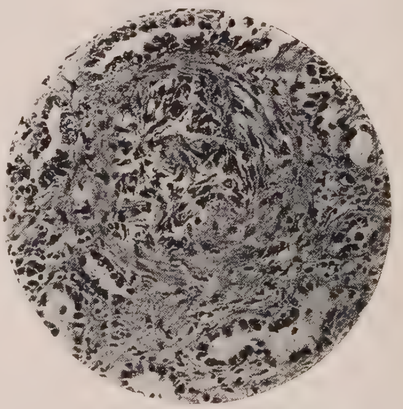

FIG. 418—Late stage of Glomerular Lesion in Subacute Nephritis.

A Malpighian body has been replaced by young connective tissue and is in process of disappearance. × 200.

embedded in the connective tissue, whilst in the intervening areas they are dilated and lined with a low or even flattened epithelium; they may contain albuminous material or some catarrh may be present. Occasionally the epithelium of the dilated tubules may show changes indicating a compensatory hypertrophy (Fig. 419), as may also some glomeruli. The arteries show various degrees of thickening with hypertrophy of media and elastic tissue, and intimal thickening is often a prominent feature in the small arterioles.

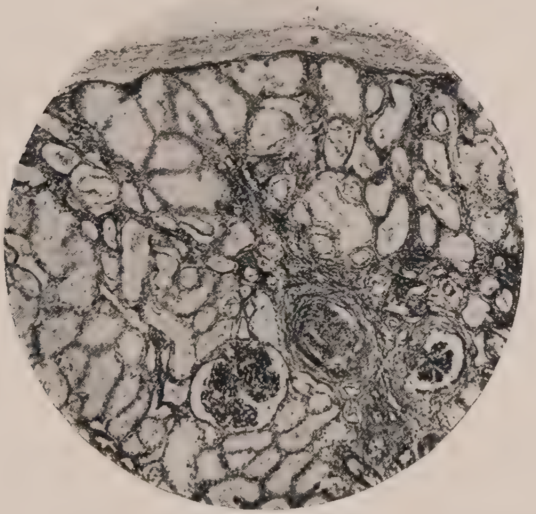

FIG. 419.—Kidney in Chronic Glomerulo-Nephritis of focal type, showing fibrotic change and area of dilated tubules. × 40.

Clinical Features. Chronic glomerulonephritis is essentially characterised by increasing failure to concentrate urea and by its retention. The blood urea is accordingly raised and may reach a high level. Hypertension is also a marked feature and is accompanied by cardiac hypertrophy and the usual arterial changes. There is usually polyuria and the urine is pale and as a rule contains little or no albumin. Death usually occurs from uræmia or from a mixture of renal and cardiac failure. Cerebral hæmorrhage occasionally occurs but this is not so common as in hypertensive nephrosclerosis. As has been mentioned, the condition may follow on hydræmic nephritis and then the features of oliguria, marked albuminuria, etc., are gradually replaced by those above described.

Kidney Lesions in Pregnancy.—In this condition lesions often occur and the effects vary greatly. There may be merely some albuminuria with a few casts, or again more marked urinary changes are attended with some œdema; the condition usually disappears at the end of pregnancy. In some cases, however, serious effects result. In such cases elevation of the blood pressure may occur and be followed by eclampsia in which the convulsions are of the hypertensive type and apparently due to cerebral anæmia brought about by angiospasm. In cases of eclampsia it has now been established that glomerular lesions are present. The affection of the glomeruli is a general one ; they are swollen and denser in appearance and there is great diminution or absence of blood corpuscles in them. There is a narrowing or closure of capillary loops owing to thickening of their walls and swelling of endothelial cells. These changes indicate interference with the blood flow through the glomeruli. Tubular changes are probably a secondary result. The cause of the kidney lesion is unknown, as is also that which leads to eclampsia.

In a certain proportion of eclamptic cases, what is known as symmetric cortical necrosis is met with. The cortex of both kidneys has the appearance of infarction, there being dull yellowish areas bordered by deep congestion and hæmorrhage. The superficial cortex is that chiefly affected (Fig. 420). The cause of the necrosis is clearly a circulatory disturbance, but the nature of this has been the subject of much discussion. Shaw Dunn has, however, adduced strong evidence that the initial change is extreme dilatation of the glomerular capillaries with slowing of the blood stream and loss of plasma, leading ultimately to complete stasis. This will lead to cutting off of the blood supply to the tubules and necrosis of their epithelium. It will also act back on the arteries, which in consequence become dilated, whilst their walls suffer varying degrees of necrotic change with a certain amount of thrombosis. In these ways, the circulation through the area of the cortex implicated is brought to a standstill.

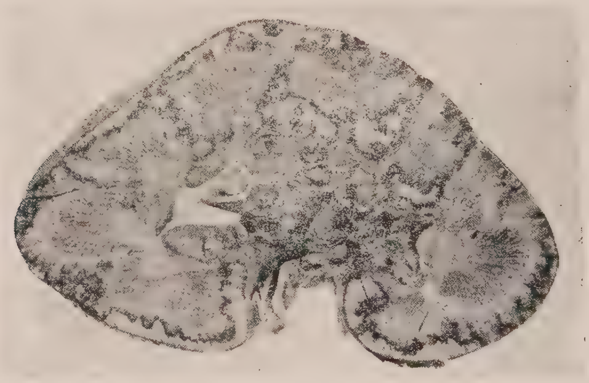

Fig. 420.—Extensive Infarction of the Kidney from a case of Puerperal Eclampsia ; the pale necrotic areas with hæmorrhagic margins are well shown. (J. H. T.) × $\frac{2}{3}$.

In a fairly large proportion of cases of cortical necrosis retro-placental hæmorrhage has been present. The effects of such a condition will be to cause a lowering of the blood pressure and it is conceivable that this occurring when there is already embarrassment of the circulation may be the means of increasing the circulatory disturbance in the glomeruli and precipitating the result.

DEGENERATIVE OR TUBULAR NEPHRITIS

Acute Tubular Damage and Tubular Nephritis. Under this heading we may group conditions in which there are varying degrees of tubular damage, which may or may not be attended with functional defect. As has been previously stated, all degrees of such damage from cloudy swelling to necrosis and desquamation of cells, are met with in infections such as septic states and septicæmia, diphtheria, lobar pneumonia, typhoid, etc., and may be accompanied merely by albuminuria—'febrile albuminuria.' In some infections, notably in yellow fever and cholera, the albuminuria may be of marked degree and associated with oliguria and casts ; sometimes actual suppression occurs. Marked tubular damage amounting to necrosis may be caused likewise by various poisons such as carbolic acid, arsenic, cantharides and also metallic salts such as corrosive sublimate, salts of uranium and chromium, oxalates (Shaw Dunn) ; and certain of these may lead to urea retention in addition. In cases of corrosive sublimate poisoning in the human subject, for instance, there is found in fatal cases much necrosis of tubular epithelium (Fig. 421) and this may be followed by calcification ; urea retention and oliguria are often marked.

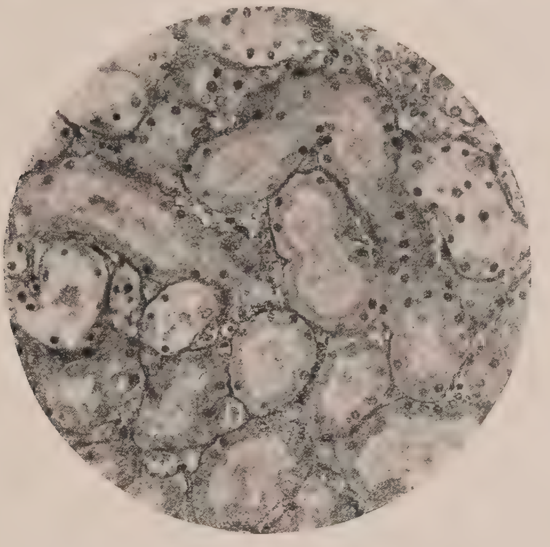

FIG. 421.—Kidney from a case of Corrosive Sublimate Poisoning, showing desquamation and early necrotic changes in the tubules. × 250.

The naked-eye appearances in such conditions are due chiefly to swelling of the tubules. Accordingly, the kidneys are somewhat swollen and tense and, on section, the substance bulges on account of the tension. For the same reason, the capillaries of the cortex contain little blood, and thus the cortex has a pale, greyish-pink colour and a rather blurred appearance. On the other hand, the medulla is often intensely congested, and contrasts markedly with the cortex. Occasionally, minute petechiæ are present in the substance and on the surface of the organ. If the condition has lasted for some time, there may be slight yellowish mottling in the cortex owing to the occurrence of secondary fatty degeneration.

In all such conditions the glomeruli are free from distinct inflammatory change and it is generally believed that if a fatal result does not follow, the tubular damage is usually effectively repaired. At any rate there is not clear evidence that any form of Bright's disease results, though the possibility of this cannot be excluded. It must be borne in mind, however, that in animals the damage to the kidneys produced by metallic salts is often followed by incomplete repair, and patchy fibrotic atrophy and irregularity of the surface may result.

Other Forms of Nephritis

Embolic Nephritis. This is a *distinct type of nephritis* which is not uncommon in cases of subacute endocarditis caused by streptococci, especially the streptococcus viridans. It thus appears clinically as a complication of that disease rather than as a primary kidney affection. The kidneys are enlarged to a varying extent, their surface is smooth and numerous small hæmorrhages are seen on it, while the cortex on section shows a reddish mottling owing to congestion and hæmorrhages on a somewhat pale background. In some cases hæmorrhages are a prominent feature, and the pyramids may be of a deep red colour owing to the presence of blood in the collecting tubules.

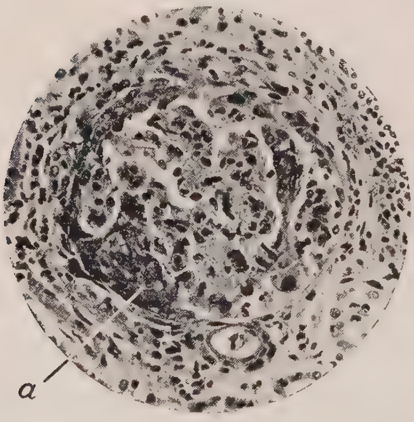

Fig. 422.—Malpighian body in Embolic Nephritis, showing hyaline patch of Necrosis (*a*), also Leucocyte Infiltration and commencing proliferation of Epithelium under Capsule. × 200.

On Microscopic Examination, the essential change is seen to be an *irregular affection of glomeruli*, some showing severe lesions whilst others are free. Furthermore, the lesion in the individual glomeruli is of patchy character. In an affected glomerulus there is often an area of hyaline necrosis which has started from a capillary and has then involved the surrounding tissue, whilst in the part beyond there is inflammatory reaction—swelling and proliferation of endothelial cells along with infiltration of leucocytes (Fig. 422). Blood or exudate with leucocytes is often present within the capsule of Bowman. The tubules may show a varying degree of catarrh, and many of them contain blood, derived chiefly from the glomeruli. It has been shown in some cases that the damage to the glomeruli is the result of the streptococci settling in their capillaries, though frequently no organisms can be found. Hæmaturia is usually present and may be a marked feature. Were recovery to occur, as is possible in mild cases, patchy overgrowth of connective tissue would result.

Acute Interstitial Nephritis. This is a comparatively infrequent though very interesting lesion. The most frequent cause is scarlatina, in which disease it occurs at a somewhat earlier stage than the more common glomerulonephritis—usually within the first fortnight. It is met with also in diphtheria and various septic conditions. It is not possible to say why two distinct types of nephritis should occur in scarlatina, but it is supposed by some that the interstitial type is specially related to mixed infections. The essential change in acute interstitial nephritis is an infiltration of the connective tissue of the organ by non-granular leucocytes (Fig. 423). These are chiefly lymphocytes, mono-nuclears and plasma cells, in some of which mitotic figures may be seen; eosinophile cells and a few polymorphonuclear leucocytes may be present. The infiltration occurs usually in a diffuse manner in the medulla and is specially marked in the boundary zone, where the tubules may be widely separated. In the cortex, it extends along the interlobular vessels, diminishing in an outward direction, and occurs also in patches which are specially in relation to the glomerular arterioles. It is of interest to note that in most cases described no organisms have been found in the lesions, which are of a generalised nature. The glomeruli and usually the tubules may be free from any noteworthy change; and with this there is to be related the fact that albumin may be absent from the urine or present in only a small amount.

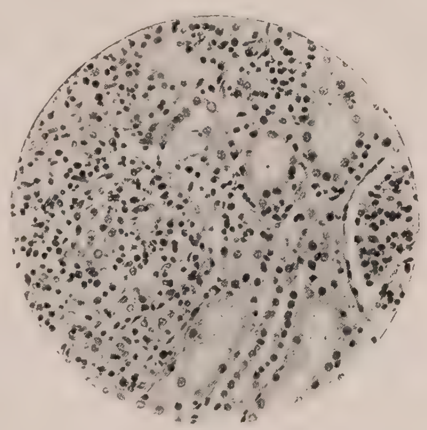

FIG. 423.—Acute Interstitial Nephritis, showing the abundant cellular Infiltration between the Tubules. × 200.

The kidneys in acute interstitial nephritis tend to be swollen, tense and rather soft, and the cut surface bulges somewhat. The medulla and boundary zone are paler than the normal and have a somewhat blurred appearance, whilst more superficially in the cortex, lines of irregular congestion alternate with the pale greyish tissue. These appearances are due to the leucocytic infiltration described, along with congestion which varies in amount; occasionally minute hæmorrhages may be present. It is of interest to note that the pancreas and liver may also show cellular infiltration.

It is not possible to speak definitely with regard to the subsequent course of this lesion in non-fatal cases. An absorption of the leucocytes with return to normal is a possibility, but it is quite likely that overgrowth of connective tissue, corresponding with the leucocyte distribution, may follow; that is, a form of subacute and chronic nephritis *may* be the result. It is further to be noted that acute interstitial changes are met with in pyelonephritis and some of the cases described as acute interstitial nephritis may be of that nature.

Hæmorrhagic Nephritis of Childhood. This type is confined almost exclusively to childhood and is characterised by marked hæmaturia, with scanty casts and slight oliguria. Œdema is generally limited to the periorbital tissues and constitutional disturbance is mild. The prognosis is usually favourable. There is marked vascular engorgement of both cortex and medulla of the kidneys which are swollen and deep red in colour. Much hæmorrhage is found in Bowman's capsule and in the tubules. Iron pigment is often present in the cells of the tubules and interstitial tissue. There is slight proliferation of the capillary endothelium of the glomeruli, with some infiltration of polymorphs; the cells of the convoluted tubules show slight degenerative change. The lesion is usually of focal nature, but occasionally is diffuse. Its etiology is unknown.

NEPHROSCLEROSIS—PRIMARY RENAL FIBROSIS

Nephrosclerosis or primary renal fibrosis includes fibrotic changes in the kidney which are due to arterial disease. (The term 'primary' merely means that the condition is not secondary to previous nephritis.) In by far the most important type, essential hypertension is present and the arterial changes are those of arteriosclerosis. The etiology of the latter has already been discussed and the conclusion which appears warranted is that the changes in the arterial tree are the result of the hypertension. Thus we have the sequence of events, (*a*) essential hypertension, (*b*) arteriosclerosis, (*c*) kidney damage and fibrosis. The damage to the kidney varies greatly in degree. In the majority of cases there is no serious impairment of kidney function and accordingly the term 'benign nephrosclerosis' may suitably be applied, but in others the vascular disturbance is greater and more rapidly produced. Advancing renal insufficiency often results and ultimately leads to death. Thus a 'malignant nephrosclerosis' is now recognised. Whilst hypertensive nephrosclerosis usually corresponds to one of the two types mentioned, the difference is one of degree and intermediate examples are met with.

In a less important type of nephrosclerosis there is no hypertension and the arterial changes are mainly degenerative; they represent an intensification of those met with in old age. These types may be put in tabular form :—

I. Nephrosclerosis with Hypertension or, Hypertensive Nephrosclerosis (*a*) Benigh type : (*b*) Malignant type.
II. Nephrosclerosis without Hypertension or Senile Nephrosclerosis.

I. Hypertensive Nephrosclerosis : (a) Benign Type.

The term hypertensive nephrosclerosis is on the whole the most suitable. It has the disadvantage that in some cases there is little or no set fibrosis or sclerosis in the kidneys as the result of changes in the arterial tree. The only alternative is to speak of 'the kidneys in essential hypertension'; an expression which is comprehensive enough but not informative as to structural changes.

The ordinary clinical picture here is one of essential hypertension, arteriosclerosis and hypertrophy of the left ventricle. (The term 'benign' applies only to the effects on the kidneys.) Patients with such a syndrome often die from cerebral hæmorrhage and in such cases the state of the kidneys varies greatly. At one end of the series we have kidneys of full size and little changed in appearance; at the other end a granular contracted kidney. The great variation in the state of the kidneys depends on the extent to which the minute arteries in the kidneys are affected as the result of the hypertension.

In our experience it is not a rare occurrence to find in essential hypertension large kidneys with a practically smooth surface; sometimes their weight is above the normal. On microscopic examination hypertrophic and fibrotic changes are found to be marked in the larger and medium sized arteries, whilst hyaline change is present in a few of the arterioles. In relation to the latter there may be a small amount of hyaline change with sclerosis of the related glomeruli, but sometimes practically none. Kidneys in such a state are examples where the minute arterioles have suffered a minimum of damage from the hypertension.

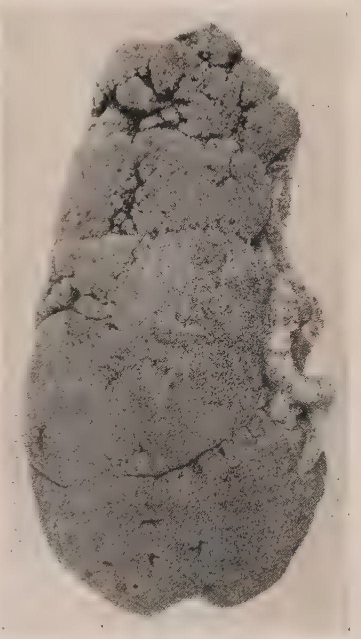

FIG. 424.—*Nephrosclerosis* of irregular type from a case of Arteriosclerosis with Hypertension.

Note the greatly sclerosed renal artery. × $\frac{2}{3}$.

In the majority of cases of benign hypertension, the kidneys are in some stage of irregular contraction and fibrosis, such as is illustrated in Fig. 424, and of course there are great variations in such a condition. There may be merely patches of commencing granularity with some capsular adhesions, or there may be areas of irregularity with distinct shrinkage, especially along the convex border of the organ. Sometimes, however, the affection of the arteries and arterioles is of a general kind and of marked degree throughout both kidneys, and then a *granular contracted kidney* results. In all such cases the sequence of events is the same—an advancing implication of arterioles, hyaline change and sclerosis of glomeruli, atrophy of tubules, secondary fibrosis. There is in fact a progressive loss of nephrons. This type of granular kidney has occupied so important a place in medical literature that a short account of a typical case may be given.

Primary Granular Contracted Kidney—Genuine Schrumpfniere of German writers. In this form the granularity of the organ is pretty even in distribution, and the colour is usually red. The consistence is moderately firm and elastic. The capsule is thickened but not markedly adherent and on its being stripped the surface is seen to be granular and of mottled appearance. The elevations in the granular surface are somewhat pale while the depressions are of red colour. On section, the cortex is found to be atrophied in varying degree and the normal markings have disappeared, the parenchyma presenting a confused reddish mottling or stippling. The walls of the arteries are thickened and stand out prominently. This is notably the case in the boundary zone where the vesses appear to be both increased in size and more numerous, owing to the fact that they are often tortuous and thus appear several times in the section. The medulla also is diminished in thickness, but less proportionately than the cortex, and the pelvic fat is increased in amount to compensate for the general atrophy. The renal artery and its branches in the hilum are the seat of distinct arteriosclerosis and are abnormally large and prominent. The term 'red granular' used to be applied to this type of kidney in contrast to the 'pale contracted' kidney of chronic nephritis. It is, however, often impossible to say without microscopic examination whether a granular contracted kidney is of the primary or secondary type.

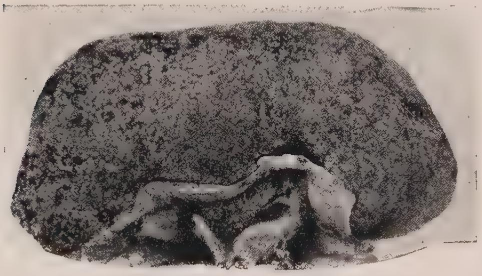

FIG. 425.—Granular Contracted Kidney of primary type from a case of chronic Lead Poisoning.

Note the granular surface. ¾.

MICROSCOPIC EXAMINATION shows that in the cortex there are areas of fibrosis alternating with portions less affected. The former, owing to the contraction which occurs, correspond to the depressions, and in them the connective tissue growth is seen to be definitely related to the intralobular arteries. These vessels are tortuous and have thickened walls which are more or less sclerotic and may show fatty change; their connective tissue is sometimes hyaline, or a more distinct endarteritis may be present. In the small arterioles hyaline change is usually a prominent feature (Fig. 426). All stages of diminution of the lumen, down to complete closure of the minute twigs, may be seen. The glomeruli are gathered together in the connective tissue around the arteries, and are quite irregular in their arrangement. Some of them appear comparatively healthy,

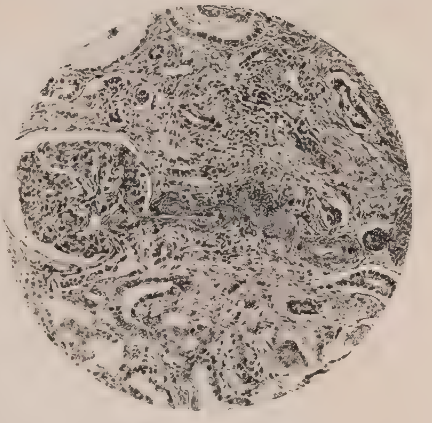

FIG. 426.—Primary Renal Fibrosis, showing great hyaline thickening of afferent Vessel passing to Malpighian body. (J. S. D.) × 100.

whilst others are sclerosed and changed into small balls of hyaline appearance, enclosed in a thickened and closely applied capsule of hyaline fibrous tissue; in others again, the change is seen in various stages (Fig. 427).

In the connective tissue around, the tubules are for the most part atrophied and lined with small cubical cells. Patches of lymphocytic infiltration may be present in the fibrous tissue. On the other hand, the intervening areas, corresponding to the elevations, are composed chiefly of tubules, between which there is comparatively little increase of fibrous tissue. The tubules are often dilated and the epithelium tends to be of the cubical type; it occasionally may show evidence of compensatory hypertrophy. There are usually present colloid casts, which are often

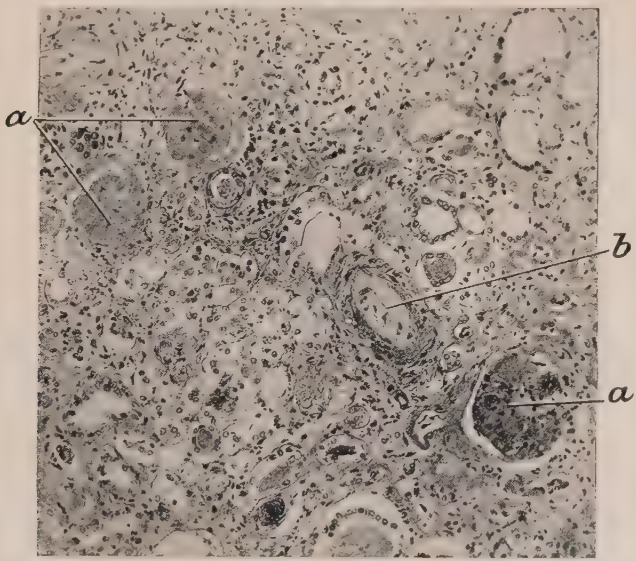

FIG. 427.—Primary Contracted Kidney, showing Fibrosis with Atrophy of Structures.

a, glomeruli in various stages of hyaline change sclerosis; *b*, arteriole undergoing obliteration. × 120.

very abundant in the collecting tubules. The larger arteries show the usual hypertrophic changes and resulting fibrosis.

The account given is one of a primary granular contracted kidney of very chronic type. In many cases, however, some of the features of the malignant type are present in addition.

Clinical Effects. Hypertension with nephrosclerosis of the benign type may last for years without appreciably affecting the health. There may be some polyuria with slight albuminuria or without albuminuria, but there is no impairment of renal function with rise in the blood urea. Death usually occurs not from uræmia but in some other way ; for example, it may be due to cerebral hæmorrhage and in fact benign nephrosclerosis is the commonest cause of its occurrence. In other cases the hypertrophied heart fails and the case becomes one of cardiac decompensation with œdema, etc. Again, there may be development of the malignant type or imflammatory change may be superadded. Of course, death may occur from intercurrent affections and the renal lesion may be an accidental finding.

The *etiology* of primary granular contracted kidney is simply that of essential hypertension, the effects of which vary both in distribution and degree. It is not possible to say why in some cases the kidneys almost escape whilst in others there is an almost general affection of their substance. The granular kidney has been generally related by writers to gout and lead poisoning ; but these, at most, can account for only a part of the causation. Our experience is that this type of lesion in its characteristic form is less common than it used to be.

Hypertensive Nephrosclerosis. (*b*) **Malignant Type.** The affection usually develops at an earlier period than the ordinary benign type, often before the age of forty-five. The size of the kidneys varies but is usually not much diminished, in fact they may be of normal size. The surface is uneven but usually not definitely granular, and shows some ill-defined reddish areas or spots due to congestion and hæmorrhage ; on section similar areas are seen in the cortex, often running in a perpendicular way. The renal artery and its branches show marked sclerosis. On mircoscopic examination severe arterial lesions are found. The small arteries show great intimal thickening due to concentric layers of connective tissue ; the lumina are in consequence much diminished. In the arterioles, in addition to the usual hyaline change, there may also be a fibrinoid necrosis of the wall and a varying amount of necrosis may extend into the root of the glomeruli ; thrombosis of glomerular capillaries may result (Fig. 428). The glomerular affection is very uneven. There is an irregular and intense capillary congestion with a varying amount of hæmorrhage, and the latter may be present also in the glomeruli ; secondary proliferation of capsular epithelium may follow. Patches of interstitial change, cellular or fibrotic, are present. Though recent leucocytic emigration is present we consider this a secondary phenomenon. The condition as a whole is not inflammatory, as was at one time believed, but represents a profound disturbance of the circulation due to varying degrees of arterial obstruction, and the congestion represents an imperfect circulation with a stagnant condition of blood flow in consequence. In fact, we may regard the state of the circulation as one approaching multiple minute infarctions, these resulting from imperfect blood supply. One other point of importance is that the arterial changes are not confined to the kidneys but are present in other organs. They vary much in distribution and extent in different cases.

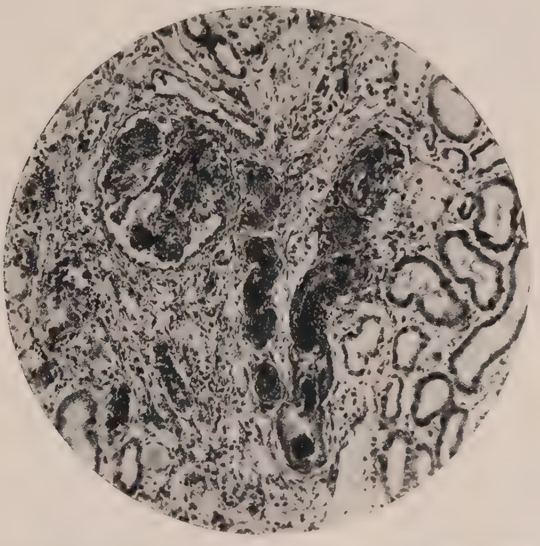

Fig. 428.—Kidney in malignant nephrosclerosis, showing fibrinoid necrosis in intralobular artery spreading to afferent arterioles and aglomerulus.

Clinical Effects. The early stage of the disease may be said to be symptomless but the development of renal damage brings with it important functional defects. In some cases the symptoms develop in a case in which hypertension has been recognised to exist for a long time ; in others the period of known disease is relatively short. The degree of cardiac enlargement affords some idea as to the duration of the case. Along with the hypertension, which is usually marked, there is elevation of the blood urea and this progresses. Albumin appears in the urine and may be abundant ; there may be also red corpuscles. The symptoms of renal insufficiency such as headache, vomiting, convulsions, impairment of vision, etc., appear. Retinal changes, especially papillœdema, are present. Death occurs from uræmia or from a mixture of cardiac and renal failure.

It will be seen from this account that the symptoms of malignant nephrosclerosis resemble those of chronic nephritis with renal insufficiency and from the clinical point of view are not distinguishable.

But the two conditions are different in their etiology and mode of evolution, and it is merely a case of the same end result being reached by two different routes. We have held this view from histological examination and it may be held to be established by the work of Goldblatt and others on hypertension, as already described (p. 297). In some instances only hyaline arteriosclerosis, in others serious necrotic damage to the walls of small arteries results.

2. **Nephrosclerosis without Hypertension.**

The Senile Contracted Kidney. This is a not uncommon lesion in old people and may be regarded as secondary to senile arterial disease. Increased arterial pressure and hypertrophy of the left ventricle are usually absent, and there may be no noticeable change in the urine; the condition is thus sometimes unsuspected during life. It is really a condition of minor importance.

The kidneys are diminished in size and may be very small; one is often more shrunken than the other. The capsule is, as a rule, only a little thickened and adherent, and when stripped, leaves a surface which is very irregular. There may be depressed areas of considerable size which have a finely granular or almost smooth surface and a red colour, whilst the elevated portions are paler. The essential point is that certain portions of the kidney are extremely atrophied and these atrophied parts are very unevenly distributed. On section of the organ, the atrophy is seen to be very irregular; in the depressed areas the cortex may be reduced to a mere line, while in other parts it is less affected. Microscopic examination shows that in the atrophied areas there are groups of sclerosed Malpighian bodies irregularly drawn together along with atrophied tubules, but the overgrowth of the connective tissue is proportionately less than in the forms previously described. In other parts the renal tissue may be relatively unaffected. Atheroma is commonly present in the larger arterial branches, whilst the smaller twigs show much hyaline thickening which leads to diminution of the lumen. The changes in the kidneys are essentially the result of those in the renal arteries and their branches, and their irregular distribution is due to the varying degree in which the branches are affected. It is remarkable how much destruction of kidney substance may occur in such cases without distinct symptoms resulting.

Other Causes of Fibrosis. Other conditions than those mentioned may lead to granularity or irregularity of the kidneys. An important example is chronic pyelonephritis in which varying degrees of shrinkage and granularity are met with; one or both kidneys may be affected. Hypertension commonly results and this may be of the malignant type (p. 703). Again, in polyarteritis nodosa of chronic type the lesions of the arteries may lead to atrophic change or actual infarctions with corresponding effects on the kidney structure (p. 309). Lastly, considerable irregularity may be produced by the healing of multiple infarctions of the ordinary type seen in cardiac cases.

Effects of Nephritis and of Nephrosclerosis

The conditions associated with nephritis are of great interest, and constitute a very important chapter in relation to clinical medicine, as practically every organ in the body may be involved secondarily and have its function interfered with. Many of the chief facts have already been mentioned but a general survey may be given.

Changes in the Urine. These are of two kinds. (*a*) On the one hand, as a result of the lesions in the kidneys, abnormal substances and cellular elements appear in the urine; and (*b*) on the other hand, there is interference with the excretory function, with retention of various substances—that is, there is renal insufficiency in varying degree.

(*a*) *Albuminuria* or, more accurately, *proteinuria*, is seen to be one of the important features in certain forms of Bright's disease. In acute glomerulo-nephritis it is associated with different degrees of oliguria and with the presence in the urine of casts along with red corpuscles and leucocytes. In the hydræmic of subacute nephritis and in lipoid nephrosis, including the amyloid type, massive albuminuria is the rule in association with distinct oliguria, but here the absence or paucity of red corpuscles is a feature. In fact we may say that chronic oliguria is practically always accompanied by albuminuria. On the other hand, in chronic nephritis albumin in the urine is scanty or absent, while polyuria with low specific gravity of urine is present, and the same holds in the benign type of essential hypertension. In the malignant type of the latter condition, however, the severe structural changes in the kidneys are attended by albuminuria, escape of red corpuscles, etc. These are the main facts as to the conditions of occurrence of albuminuria to be considered.

In 'albuminuria' the protein includes both serum albumin and serum globulin, the proportion of which may vary at different stages of nephritis. In hydræmic subacute glomerulo-nephritis and lipoid nephrosis, however, the proportion of albumin in the urine is greatly raised. This is of importance in connection with the œdema occurring in these conditions as it leads to a correspondingly greater fall in the blood plasma of albumin as compared with globulin; seeing that the albumin molecule is smaller than the globulin, the colloid osmotic pressure of the blood is lowered to a greater degree than if the globulin were equally affected (p. 50). The source of the protein is essentially an escape through the damaged glomerular capillaries; though there may be some escape through the basement membrane of tubules whose epithelium has been lost or damaged. If the modern theory of filtration and re-absorption be accepted it will be seen that the concentration of protein in the urine in no way represents that in the glomerular filtrate. Seeing that the filtrate is concentrated about one hundred times, the amount of protein in the filtrate in nephrotic conditions need only be quite small. The hyaline casts so often seen in the urine in nephritis are apparently formed from concentration of protein in its passage down the tubules, and the hyaline droplets in the cells of the tubules by re-absorption of the protein. It must be understood, however, that the presence of albuminuria does not show that nephritis is present. A small amount of albumen is met with in the urine of a small proportion of healthy adults, especially in the earlier periods of adult life, and has no pathological significance; further, albuminuria is sometimes produced by severe physical exertion and thereafter passes off.

Red corpuscles are to be found on microscopic examination in the acuter stages of nephritis, and the amount of blood is often sufficient to give the urine a smoky appearance or even a reddish colour. In some cases, known as hæmorrhagic nephritis, the escape of blood is very great, and the urine comes to have a dark red colour. Severe hæmorrhage sometimes occurs in nephritis when some infective condition becomes superadded, and it is not uncommon in the embolic nephritis of subacute bacterial endocarditis (p. 668). Hæmaturia may occur also in malignant nephrosclerosis owing to disturbances of the renal circulation. The source of the blood is chiefly glomerular though there may be some escape from damaged tubules. It may be noted that in patients recovering from acute nephritis a few red corpuscles may persist in the urine for a remarkable period; in fact we have often found a few when albumin had practically disappeared. On the other hand, in ' lipoid nephrosis ' the absence of blood in the urine is one of the characteristic features. *Leucocytes* also occur in the urine in varying numbers, especially in the acuter stages of glomerulo-nephritis.

In view of the description given above, the presence of different kinds of *casts* in the urine can be readily understood. These are formed of abnormal substances within the tubules, down which they are then passed. They may be *hyaline*, that is, transparent and structureless, and apparently the result of concentration of protein in the filtrate as it passes down the tubules; *granular*, composed of the granular remains of cells; *epithelial* and *fatty*, both ordinary neutral fat and doubly refracting fat being met with. The two first usually preponderate in the early stages, the two last when the condition becomes less acute; mixed forms also are met with *Blood* casts, composed of red corpuscles, occur when there is hæmorrhage into the tubules. In the chronic lesions (primary or secondary) *colloid* casts are often present along with others. The colloid casts are of homogeneous appearance, larger and more highly refracting than the hyaline forms, and appear to be composed chiefly of derivatives from the damaged epithelium. They may be seen in large numbers in sections of kidneys at this stage; they abound also in amyloid kidneys.

(*b*) With regard to *interference with excretory function*, this affects all the constituents of the urine, but it is convenient to consider it in relation to urea excretion on the one hand and excretion of water and salt on the other. This corresponds with the two main types of subacute nephritis described above.

Retention of urea is of prime importance. The amount in the urine is diminished in various conditions and along with this the blood urea is increased. The percentage or head of urea in the blood is, however, the more important as an indication of the state of the kidneys. A raised blood urea implies an increased concentration of urea in the glomerular filtrate and this may result in a deceptive amount in the urine. Normally the blood urea is about 25–30 mg. per 100 c.c., but in chronic nephritis it may rise to 200 mg. and sometimes much higher. The conditions to be considered in which there is urea retention are chiefly (1) acute nephritis, in which it is of moderate degree but variable, (2) the azotæmic type of subacute nephritis and chronic nephritis, reaching a high level in the latter, and (3) malignant hypertension. There are, however, some others.

Retention of water is accompanied by salt retention, though not always in equal proportion. Here the chief conditions are acute nephritis, in which again we see a moderate and variable degree, and the hydræmic type of subacute nephritis where it is of marked degree and in association with massive albuminuria and œdema. There is also to be considered an increased output of water and salt, that is polyuria. This occurs notably in chronic nephritis and in the benign type of hypertension. The basis of these disturbances may now be considered.

The Basis of Renal Insufficiency.[1] The functions of the kidneys are of two chief kinds. On the one hand there is the excretory function directed towards keeping the chemical constitution of the blood up to a normal standard, and on the other the maintenance of a standard blood volume. In both of these the kidneys play a dominant role. Both functions undergo disturbances in disease, and we have to consider how these are brought about and also their significance. In doing so we go on the principle that an organ proceeds in what may be called a purpose-like way to meet abnormal conditions.

The modern view with regard to urine formation is now so well supported that we shall adopt it in discussing the subject. An account of this need not be given but it is as well to keep before us the essential facts. We have to deal with (*a*) a process of filtration by the glomeruli resulting in a filtrate which is essentially a protein-free plasma, and (*b*) a process of re-absorption by the tubules of water and various substances in solution, urine being the final product. The degree to which different substances are absorbed varies greatly, but one all-important fact is that the renal epithelium is practically impervious to urea, which accordingly is gradually concentrated by the absorption of water during the passage of the filtrate down the tubules.

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[1] A detailed account of this subject will be found in H. MacLean's *Modern Methods in the Diagnosis and Treatment of Renal Disease*, London, 1921.

The structural unit is the nephron, a glomerulus with its related tubule, and the work of the kidney may be said to be done by an assemblage of nephrons. A very important observation made by Richards on the frog's kidney is that normally only a fraction of the nephrons are in a state of action at one time, and it is justifiable to believe that the same holds with regard to the human kidney. Accordingly, there is what we may call reserve filtering capacity and when some glomeruli have their function impaired or are thrown out of action, this may be compensated for by others. But we can imagine so extensive an affection of the tufts that this is not possible and the total glomerular filtrate is necessarily reduced, even though the unaffected glomeruli have some capacity for hypertrophy.

In connection with the histological changes in disease, two points are of importance. One is that the functional activity of a tubule depends on its receiving filtrate from its glomerulus, and if the glomerulus is permanently put out of action the tubule undergoes atrophy. Tubular atrophy is frequently produced in this way. The other point is that practically all the blood passing through the intertubular plexus has previously passed through the glomeruli. Lesions in the latter may thus interfere with the blood supply to the tubules and affect their nutrition. Tubular change may thus be secondary to glomerular change. There is, however, here not the same definite relation of a glomerulus to its tubule, as the blood from various glomeruli mixes in the intertubular plexus.

We have already referred to two types of glomerulonephritis, the *azotæmic* attended by low concentration of urea with liability to its retention and raised blood pressure, and the *hydræmic* type in which oliguria and œdema are the outstanding features. We may now consider some aspects of these functional disturbances.

Urea retention may result in two chief ways. In the first place it may result from a deficient total glomerular filtrate or, in the second place, it may be due to some disturbance in the process of concentration of urea during the passage of the filtrate down the tubules. In order that the blood urea be kept at a normal level it is essential that a certain amount be continuously removed and this, of course, can only be effected by sufficiency of glomerular filtrate. This in its turn implies sufficient circulation of blood through the glomeruli. Interference with blood flow through some glomeruli may be compensated for by increased activity of others, but a stage may be reached in which this compensatory mechanism is insufficient ; and further in some conditions practically all the glomeruli may be affected. This is evidently the case in acute diffuse glomerulonephritis, where the extensive intracapillary proliferation would seem to imply serious interference with the blood supply and filtration. The histological changes in some subacute cases would point to the same result. To what extent deficiency of total filtrate occurs, it is not possible to say ; probably to a less extent than appears, otherwise the tubules which receive their blood supply from the glomeruli, would show more evidence of damage than they may do in acute glomerulonephritis.

There is clear evidence that diminished concentration and retention of urea may be due to tubular damage. In the normal state, as the result of absorption of water by the tubules, the concentration of urea in the filtrate increases in its passage downwards until its concentration in the urine is reached. This implies work done by the epithelium against the physical force of diffusion. Thus, if the concentration of urea be added to by the oral administration of urea, the absorption of water is interfered with, and the urea acts as a diuretic. Accordingly, when the cells of the tubules are lost by catarrh or necrosis, the power of retaining urea in the tubules is impaired and urea passes back into the blood. In fact if there were no epithelial barrier all the urea would pass back into the capillary blood. This is the view adopted and expounded by Shaw Dunn and is supported by much work done by him and his co-workers in various papers on experimental nephritis. They have shown that in the tubular nephritis produced by various chemical agents, corrosive sublimate, uranium nitrate, etc., in which there is no significant glomerular lesion, the urea retention which is associated with oliguria receives a satisfactory explanation on this basis. In subacute and chronic nephritis the altered character of the tubular epithelium to a more cubical type probably indicates a lowering of its function in connection with the concentration of urea. There is also diminution in the total amount of functioning epithelium. Of course, a combination of glomerular and tubular defect will be specially effective in leading to urea retention.

In the hydræmic type of subacute glomerulonephritis and lipoid nephrosis there is the important association of oliguria with satisfactory excretion of urea, and this obtains also in amyloid nephrosis and some cases of the nephritis of pregnancy. This has been a difficult problem. Shaw Dunn has offered a satisfactory explanation, which is based on the abolition of the normal intermittent action of nephrons. To take the example of lipoid nephrosis, the permanently dilated condition of the glomerular capillaries shows that this action is actually in abeyance, and as already stated, it explains the escape of protein in the filtrate. If we suppose that all the glomeruli are in action instead of, say, one in three, then as the circulation through the kidneys is not increased, the total glomerular filtrate is not increased but is distributed to all the tubules instead of, as normally, to one in three. The flow of the filtrate will be slower and the filtrate will be exposed to a greatly increased absorbing surface. Thus reabsorption in excess will result and there will be retention of salt and water. It seems to us that abnormally increased reabsorption is necessary for an explanation of the oliguria which occurs in the absence of urea retention. In experimental tubular nephritis produced by chemical agents, the retention of salt and water may be attributed, as he supposes, to the failure of the normal selecting and conducting function of the tubules owing to the damage of their cells; these substances accordingly pass back into the blood as the easiest path, but in this case urea also is reabsorbed and so retained. The same probably obtains in human diseases where there is severe tubular damage with oliguria and sometimes anuria, e.g. yellow fever, cholera, etc. Actual mechanical obstruction of tubules may also play a part.

In addition to estimation of blood urea, other tests have been introduced in the study of renal efficiency. One of these is the *urea concentration* test, in which a certain amount, usually 15 grm. of urea in a solution, is given by the mouth, and then at a certain period afterwards the percentage of urea in the urine is estimated; from this an indication is obtained as to the functional activity of the kidneys. The *urea clearance* test is rather more complicated but gives more definite information. The *diastase* test depends upon the fact that normally the kidneys excrete into the urine a starch-splitting ferment which is formed by the pancreas. In renal insufficiency, the excretion of this diastase is interfered with, and accordingly estimation of the amount of it in the urine often gives valuable information. In other methods the renal efficiency is judged of by investigating the power of the kidneys to excrete certain dyes, phenol-sulphone-phthalein being often used for the purpose.

In nephritis the *excretion of acids* by the kidneys is interfered with, but this is a subject less fully investigated. The retained acids combine with the sodium bicarbonate of the blood, and thus the so-called alkaline reserve is diminished and a form of acidosis results. There is no real change in reaction, that is, in the hydrogen ion concentration of the blood, as this depends on the relation of carbon dioxide to sodium bicarbonate, and when the latter is diminished the former is got rid of by increased respiration. This is probably the explanation of the dyspnœa which is sometimes a prominent feature in some cases of uræmia, and also of the Cheyne-Stokes respiration which sometimes develops, the latter being due to the excessive ventilation of the lungs brought about by excess of carbon dioxide. In the acidosis of nephritis there is usually no accumulation of acetone bodies, i.e. no ketosis; and no increase of ammonia nitrogen in the urine, such as occurs in the acidosis of diabetes (p. 947). In some cases of uræmia a slight increase of hydrogen ion concentration has been found, but to what extent this plays a part in the production of respiratory and other symptoms, cannot as yet be stated.

Uræmia. This term has been for long applied to a group of symptoms in Bright's disease, chiefly related to the nervous system and believed to be due in some way to the retention of excretory substances. It is now known, however, that most of the symptoms are related to the hypertensive state and may occur without any retention of urea, etc. The term hypertensive encephalopathy or pseudo-uræmia (Volhard) has accordingly been applied. In this condition the symptoms are headache, vomiting, disturbance of vision, localised or general, convulsions passing into coma and death. These symptoms are accompanied by high blood pressure and retinal changes, hæmorrhages and papillœdema. Hypertensive encephalopathy may be met with in the earlier years of life before structural arterial changes have occurred and is then often associated with œdema of the brain and a heightened cerebrospinal fluid pressure; recovery may take place. It may also occur later when there is hypertensive arterial disease. In all cases the cause is believed to be cerebral anæmia due mainly to contraction of arterioles, or angiospasm. Puerperal eclampsia is regarded as a variety of this condition. In true uræmia on the other hand, produced by the toxic action of retained products and acidosis, the symptoms form a different syndrome. The main features are vomiting and anorexia, mental dullness, muscular twitchings, but no convulsions or focal cerebral symptoms; coma often supervenes but may be long delayed. It is evident, of course, that in chronic nephritis malignant nephrosclerosis the symptoms may be a combination of the hypertensive and the true uræmic type.

Cardio-vascular Changes. Here there are two classes of cases to be considered, viz. (*a*) the class in which the kidney lesion is primary and leads to cardio-vascular changes, and (*b*) that in which the kidney is involved as part of a general arterio-sclerosis.

(*a*) At an early period in acute nephritis, the blood pressure may be distinctly raised, and this condition may persist if the kidney lesion progresses. The continued high pressure brings about the hypertrophic changes in the artery walls already described (p. 293), and fibrous change in the hypertrophied coats may follow. There occurs also hypertrophy of the left ventricle, though this rarely reaches the degree met with in primary arteriosclerosis. These cardio-vascular changes are seen in subacute nephritis of the azotæmic type or its contracted stage, and their occurrence appears to be specially related to obstruction to blood flow through the glomeruli. In subacute glomerulo-nephritis of the hydræmic type, and in ‘ lipoid nephrosis ’ the blood pressure is as a rule practically normal. Later, however, the disappearance of œdema may be accompanied by a rise of blood pressure. In fact, if in a case with the features of nephrosis there is some elevation of blood pressure, it is generally agreed that the glomeruli are distinctly damaged by inflammatory change.

The cause of the high blood pressure which may start in nephritis at an early stage, remains to be considered. In view of all the facts with regard to the conditions of occurrence of hypertension and the associated structural changes in the kidneys, it appears justifiable to regard it as of compensatory nature and brought into play in order to maintain an efficient circulation against obstruction in the glomeruli. This is supported by recent experimental work already discussed. It has been shown that mechanical constriction of the renal arteries by means of a clamp leads to effects according to the degree of constriction. Moderate constriction leads to continued hypertension unaccompanied by impairment of renal function. If, however, it is severe such impairment follows, there being accumulation of urea in the blood, ending ultimately in uræmia (Goldblatt and others). Whether, however, the hypertension is produced by a pressor substance absorbed from ischæmic renal substance, as some have supposed, remains to be determined.

The results of destruction of the kidney substance by disease vary. In cases of hydronephrosis or renal calculi with atrophy and fibrosis of the kidney substance and in chronic pyelonephritis, high blood pressure and cardiac hypertrophy often result. A certain amount of hypertrophy may be met with also in congenital cystic kidneys. On the other hand, where there is loss of kidney substance from chronic suppuration, tuberculosis, or amyloid disease, cardiac hypertrophy is absent.

(*b*) In cases where the kidneys are involved as part of a general arteriosclerosis, the cause of the essential hypertension has already been discussed (p. 297). We may repeat, however, that it is still unknown and that it is not justifiable to regard it as of renal origin. The hypertension may certainly occur with a minimum of renal change. The extensive arterial changes in the kidney, however, will in their turn interfere with the circulation and intensify the hypertension, a vicious circle being thus established.

Œdema. The nature of renal œdema has already been considered (p. 50), and we shall here only recapitulate some of the chief facts regarding its occurrence. We may add here, however, to what we have already stated that in the œdema accompanying tubular nephritis experimentally produced by chemical agents, the retention of water and salt appears to us to play the chief part, as Shaw Dunn maintains. There may be a certain amount of general œdema of the connective tissues early in acute nephritis—in fact, a puffiness round the eyes is often the first sign to be noted. It is, however, in the hydræmic type of subacute glomerulo-nephritis and in nephrosis that œdema becomes most marked, and then the skin and subcutaneous tissues become greatly swollen and tense. Associated with this, there is usually marked pallor osing to the anæmia present, and then the appearance of the patient becomes characteristic. The anæmia is of the microcytic type, and along with the changes in the corpuscular elements there is fall in the proteins with diminution of the specific gravity of the plasma. It may be added that in such cases the œdema may be present in the brain and other internal organs. The significance of these changes in the two types of renal œdema have already been discussed (p. 52). In subacute glomerulo-nephritis with azotæmia œdema is usually absent, and this is still more the case in the contracted stage of glomerulo-nephritis.

In primary renal fibrosis or nephrosclerosis œdema is absent as a rule, and may be so throughout the disease. In the later stages, when the hypertrophied heart begins to dilate, and incompetence of the valves with venous engorgement follows, œdema may appear. But in such circumstances œdema occurs first round the ankles and then spreads upwards ; it is of the cardiac type and of cardiac origin. In fact, we may say that nephrosclerosis does not cause œdema of the renal type. When, however, an acute nephritis is added to the chronic condition, as sometimes occurs, then œdema of the renal variety may appear. Accordingly, while there are the two main types of œdema, mixed types may be met with and the clinical picture is often difficult of analysis.

Inflammatory Complications, etc. Along with the marasmus and anæmia often produced by Bright's disease, there is associated a diminished resistance to bacterial invasion, and thus inflammatory conditions are comparatively common. These may affect the serous sacs and mucous membranes. Pericarditis is a fairly common complication ; and pleurisy, peritonitis and meningitis, though less frequent, also occur. Catarrh of the respiratory tract, especially bronchitis with a tendency to asthma, is met with, and pneumonic complications may ensue. Pulmonary œdema is often a terminal phenomenon, especially in cases where general œdema is present. Inflammations about the mouth occasionally lead to œdema glottidis. A common lesion of the bowel is an extreme œdema of the duodenum and upper part of the jejunum, and this appears to be related to some of the intestinal symptoms of uræmia ; it is sometimes associated with a hæmorrhagic condition. But actual enteritis may supervene, and this may be of a membranous type and may lead to ulceration of the colon. These facts show in how important a degree the general nourishment may be influenced by nephritis. Further, the occurrence of ' albuminuric retinitis ' is to be mentioned. It is seen round the optic discs in the late stages of nephritis with hypertension as well as in nephrosclerosis of the malignant type, and consists mainly of a combination of degenerative change with deposit of cholesterol fat, and of vascular disturbances, papillœdema and small hæmorrhages. The areas of degeneration are of pale appearance and are often somewhat radially arranged ; along with the hæmorrhages they give the fundus a characteristic appearance. Hæmorrhages are often a prominent feature in malignant nephrosclerosis ; in the benign type, on the other hand, there are usually no retinal changes, with the exception of a contracted condition of the arteries, and possibly a few small hæmorrhages. Albuminuric retinitis is usually regarded as a change of grave omen ; death is said to occur in many cases within a few months of its appearance.

Renal Dwarfism or Infantilism. Occasionally small fibrotic kidneys have been found associated with a state of defective growth and infantilism. Polyuria and thirst are often prominent symptoms. The bones may become affected, being unduly porous and fragile, with a tendency to spontaneous fracture and deformities. The changes in some respect resemble those of rickets and the disease is known also as 'renal rickets,' but they are slower in development and occur at a later period. While the calcium metabolism is clearly disturbed, there is no evidence that this is due to vitamin deficiency, but is in some way the result of the kidney lesion. The most reasonable explanation is that there is a failure of the kidneys to excrete phosphates and that these are passed into the bowel, causing a deviation of calcium or interfering with its absorption. Hyperplastic changes have been observed in the parathyroids, but these are in all probability of secondary origin. The etiology of the renal disease is often obscure. It is suggestive, however, in this respect that marked hypoplasia with fibrosis of the kidneys may be present at birth and lead to uræmia at a very early period (Blacklock). In some cases the renal fibrosis may be the late result of a pyelo-nephritis occurring in the early years of life. It is noteworthy that dilatation of the pelves of the kidneys and ureters has been observed in a considerable proportion of cases and this has been ascribed to spasm or achalasia at the lower end of the ureters. Various points, however, with regard to this condition are still obscure.

Amyloid Disease

The kidneys are amongst the organs most frequently affected by amyloid disease (p. 151). At an early stage there may be little change in their appearance, and the presence of amyloid is discoverable only on the application of the iodine test, or even only on microscopic examination. But as the disease increases, the kidneys undergo enlargement, and may ultimately reach a considerable size. The substance of the organs is rather firm, and when the capsule is removed, the surface is smooth and very pale, the lines of vessels standing out against the pale background. On section, the cortex shows a corresponding pallor; it has a greyish and somewhat translucent appearance, with yellowish mottling owing to fatty changes in the tubules (Fig. 429). The red medulla forms a marked contrast to the cortex though it also is somewhat paler than usual. On the application of iodine, the affected glomeruli come out prominently as rows of dark brown dots, and usually the medulla stains deeply, owing to the affected vessels. Sometimes, on account of the associated presence of interstitial change, the capsule is slightly adherent, and the cortex shows signs of shrinking. There is also a

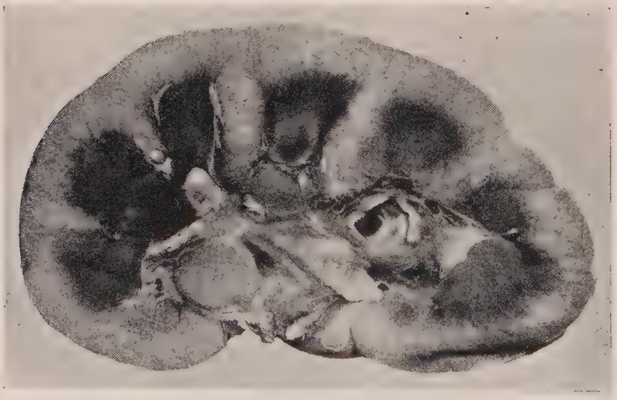

FIG. 429.—Amyloid Kidney.

Note the marked pallor of the cortex with slight mottling. × $\frac{4}{5}$.

variety of small amyloid kidney, which has all the general appearances of a granular contracted kidney, but in addition gives a marked amyloid reaction.

The earliest structures to be affected with amyloid change are the afferent arterioles and the glomerular capillaries (Fig. 430). Thence the change spreads to the inter-tubular capillaries and the other vessels. The basement membrane of the tubules becomes affected, and sometimes also the Bowman's capsules. If the amyloid disease is at all marked, important secondary changes occur in the tubules. This is due to a re-absorption of these substances from the glomerular filtrate, there being a condition of hypercholesterolæmia ; there may be a marked accumulation of myelin as well as of the ordinary fats. There are often to be seen in the tubules large homogenous casts, which probably consist chiefly of material formed by the degeneration of the epithelium ; they are conveniently called 'colloid' casts, and never give the reaction of amyloid substance. Such casts are often numerous in the urine.

There has been dispute as to the sequence of events in the case of the small amyloid kidney, but it seems to us on the whole most probable that the amyloid change has become associated with fibrosis occurring independently ; it seems unlikely that the large amyloid kidney passes into a contracted condition.

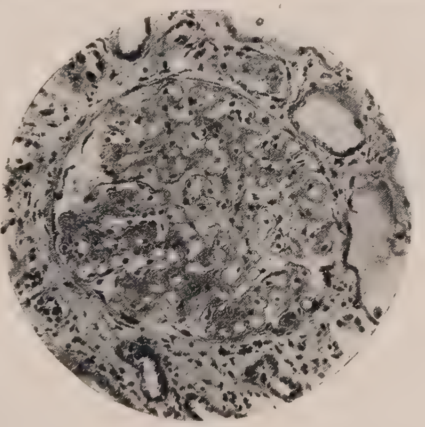

Fig. 430.—Malpighian body in Amyloid Disease of Kidney, showing the swelling and hyaline appearance of the Capillary Walls. × 200.

Functional Effects of Amyloid Disease. In the early stages of amyloid disease of the kidney the urine is increased in amount, is pale and of low specific gravity ; and there is usually little albumin. As the condition progresses, albumin increases in amount and may be very abundant, and usually the amount of urine may become markedly diminished. It is worthy of note that amyloid disease by itself does not produce elevation of the blood pressure or urea retention. General œdema of the renal type with ascites, etc., occurs not infrequently in amyloid disease and is associated with diminution of protein in the blood plasma and fall in the colloid osmotic pressure. We may summarise by saying that marked amyloid disease of the kidneys leads to the effects characteristic of lipoid nephrosis (p. 660) and the term 'amyloid type of nephrosis' has been applied. This is of considerable importance. Seeing that in amyloid disease the albuminuria and other effects depend on a primary change in the capillaries, especially of the glomeruli, it suggests that in nephrosis too the lesions in the tubules are secondary to glomerular damage, even if this may not be demonstrable by histological methods.

Suppurative Nephritis

This type of lesion is produced in two ways, viz.

A. As the result of *blood infection.* Of this again there are two main modes of occurrence, viz. (1) as part of a pyæmic condition usually produced by staphylococci, (2) as an infection by coliform bacilli chiefly in young women during pregnancy and in children.

B. As the result of an ascending inflammation from the lower urinary tract.

(A) **Blood Infection.** (1) In a general blood infection pyogenic organisms have a marked tendency to settle in the kidneys ; in fact, abscesses produced in this way are commoner there than in any other organ. If, for example, a small quantity of an emulsion of culture of staphylococcus aureus is injected into the ear-vein of a rabbit, the resulting suppurative foci are usually most numerous in the kidneys, and in human disease a corresponding distribution holds. Multiple abscesses in the kidneys are of common occurrence in acute suppurative periostitis and osteomyelitis, in acute bacterial endocarditis, in other suppurative lesions such as carbuncle, and in some cases where infection of the blood stream occurs from a comparatively trifling lesion ; in fact, the mode of infection in some cases is not discoverable. In diabetes there is a lowered resistance to pyococci and other organisms ; boils and carbuncles occur and blood infection in which the kidneys are involved sometimes leads to the fatal issue.

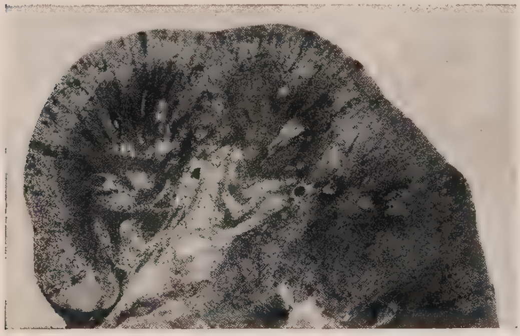

Fig. 431.—Portion of Kidney, showing multiple small Abscesses which are seen as pale areas surrounded by dark hæmorrhagic zone. $\frac{4}{5}$.

In this type of lesion *Staphylococcus aurens* is the organism most frequently concerned. The resulting abscesses are often numerous and of small size—hence often described as *miliary*. When the capsule of the kidney is stripped, they may be seen on the surface as small areas of about the size of a pin's head or larger, slightly raised and with congested or hæmorrhagic margin. When cut into, they are seen to contain small drops of pus, though at an early stage their centres are merely necrotic. They are usually in groups, and are commonest in the cortex (Fig. 431), though they occur also in the medulla, where they are oval in shape, or form pale streaks in the direction of the medullary rays. Such minute abscesses are the result of the organisms settling in the capillary walls, especially those of the glomeruli; there they grow and form plugs filling the capillaries. Occasionally they are seen in masses within a tubule, to which they have probably gained access from the corresponding glomerulus. They are carried down in the urine, and may be found there during the life of the patient.

When an arterial branch is plugged with an embolus containing organisms, a so-called septic infarction forms. A zone of suppuration may form at the margin, leading sometimes to separation of the necrosed tissue, which may afterwards undergo suppuration. In this way abscesses of considerable size and in various stages of formation may be present.

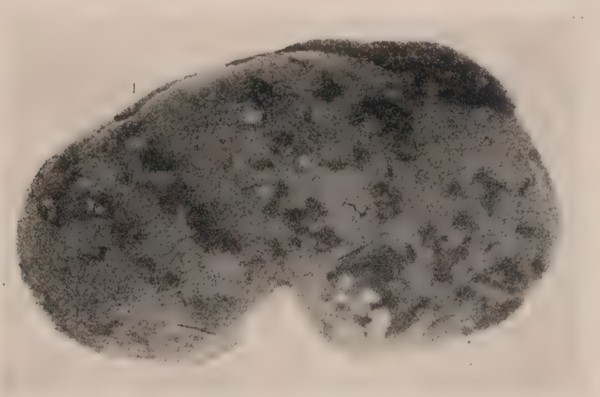

Fig. 432.—Surface view of Child's Kidney, showing characteristic changes of Pyelo-nephritis—small Abscesses and areas of Hæmorrhage.

Occasionally hæmatogenous infection leads to a *localised lesion* in one kidney. A group of abscesses may form and these afterwards become confluent, resulting in what has been called 'carbuncle of the kidney.' The condition, which is attended by pyrexia, may lead to a perinephric abscess; it may be treated surgically with success.

(2) As has been mentioned, infection by coliform bacilli may occur in connection with pregnancy and also in childhood. Usually no primary focus can be found. The organisms are arrested in the renal capillaries and suppurative changes follow. The lesions present certain differences from those due to staphylococci; they are usually larger, more ill-defined and surrounded by irregular zones of congestion (Fig. 432). In the medulla there is a characteristic focal streaking, yellowish elongated abscesses alternating with hyperæmic zones which radiate out towards the cortex. Spread of the coliform infection to the pelvis nearly always takes place, resulting in a *pyelo-*

nephritis. Later there may occur a descending infection with involvement of the bladder. Blacklock has noted that the lesions in the kidney may heal and give rise to a patchy fibrosis with resulting irregularity of the surface of the organ. This is more fully considered below.

(B) **Ascending Infection.** This is of common occurrence in cases of septic cystitis, following on stricture, enlarged prostate, calculus, etc. So long as the ureters are not dilated and the valve-like protecting mechanism at their orifices in the bladder wall is normal, bacteria do not readily spread up the ureters from the bladder. When, however, the ureters are dilated, infection becomes greatly facilitated, and an ascending inflammation may be traced. The ureter and pelvis of the kidney, on one side or both sides, then become the seat of septic inflammation. Their mucous lining becomes swollen and intensely congested, it is often the seat of hæmorrhages, and is covered with purulent secretion. If the urine is alkaline, there may be an amorphous deposit of phosphates in the pelvis, and not infrequently there is ulceration. Then the kidney substance is infected and becomes the seat of abscesses. Sometimes they form wedge-shaped collections in the pyramids and other groups in the cortex, but occasionally they may be present in the latter without any apparent involvement of the medulla. They have the same general characters as those resulting from infection by the blood. Later, a number may become confluent, and form larger abscesses, and the kidney may become riddled with these, its substance being largely destroyed. The term ‘ surgical kidney ’ is often applied to the condition of suppuration in the kidney which is the result of an ascending infection. One kidney may be affected alone, or both may be involved though usually in unequal degree. A similar lesion of a kidney may occur apart from an ascending infection, namely, when a calculus forms in the pelvis, and then bacterial infection is superadded, the organisms reaching the pelvis by means of the blood stream, or possibly by direct extension from an adjacent loop of bowel.

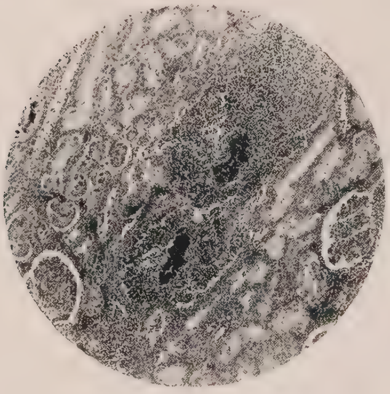

FIG. 433.—Embolic Suppurative Nephritis.

Two small abscesses are shown with masses of cocci in the central parts. × 50.

When the kidney is the seat of abscesses, the capsule may sometimes become involved and softened, and the bacteria may extend to the surrounding tissue, giving rise to a perinephritic abscess. Occasionally one kidney may be completely destroyed by suppuration, which then passes into a quiescent state ; the pus becomes inspissated and sometimes lime salts are deposited in it, while the connective tissue around becomes greatly thickened. Ultimately the appearance is not unlike that seen when a kidney is destroyed by chronic tuberculous disease (p. 693).

Microscopic examination shows that the infection of the kidney substance usually takes place by an extension of the organisms, often bacilli of the coli type, within the collecting tubules. Some writers think that extension may be by the lymphatics from the diseased pelvis ; but while suppuration may thus extend to the kidney substance, we do not think that abscesses with the characteristic distribution are produced in this way. Occasionally, however, in cases of septic cystitis, infection of the kidneys may occur by the blood stream ; the organisms may be found in the glomerular capillaries, and the usual evidence of an ascending inflammation may be absent.

SPECIFIC INFLAMMATIONS

Tuberculosis. Tuberculous lesions in the kidney may occur as part of an acute miliary tuberculosis, or may be the result of a localised infection which often leads to much destruction of the kidney tissue. In the former condition minute grey tubercles may form in the kidneys in varying numbers, but compared with those in other organs they are, as a rule, not numerous. They are irregularly distributed throughout the organ, sometimes in groups apparently related to arterial distribution. Occasionally they resemble minute abscesses, but the hyperæmic zone, usually a prominent feature in the latter, is absent or little marked. In the cortex they are of rounded form, or under the capsule somewhat wedge-shaped, but in the medulla they are oval or elongated in the direction of the medullary rays. At an early stage tubercle bacilli may sometimes be seen within the glomerular capillaries, and from them they may pass down in the tubules, and give rise to tubercles where they become arrested. In some cases of less acute nature, a few tubercles of large size and with yellow caseous centres, may be present in the kidneys and also aggregations of these may be met with.

The *local form* of renal tuberculosis often produces extensive caseation with formation of cavities, hence it used to be called *renal phthisis*. Other parts of the urinary and genital tract may become involved, the whole affection being then spoken of as *genito-urinary tuberculosis*. In the majority of cases of urinary tuberculosis the primary lesion is in a kidney, and from it the disease may extend to bladder, prostate and vesiculæ seminales, there being thus a descending infection. Thence the disease may spread along a vas deferens, and lead to enlargement and caseation in the epididymis. There has been considerable controversy as to ascending infection by the ureter, in a manner comparable with what occurs in septic disease of the urinary tract; but there seems to be no doubt that this occurs. The two commonest sites of primary tuberculosis in the male genito-urinary tract are undoubtedly the kidney and the epididymis; and when the latter is involved the disease readily spreads to the base of the bladder, producing lesions there which may involve the orifices of the ureters. The upward extension along the ureters is favoured by any cause which produces dilatation of the ureters; in fact, some authorities doubt if it occurs apart from such dilatation. In the female the Fallopian tube takes the place of the epididymis in the male as regards frequency of primary infection.

The primary lesion in the kidney is produced by a few bacilli carried by the blood stream, and are arrested in a glomerulus or in an intertubular plexus. The initial lesions are thus mainly cortical in distribution. One or more tubercle nodules are produced, and these go on enlarging and become confluent, while smaller nodules are formed around by lymphatic extension, and also by spread of the bacilli in the tubules. In some cases the whole kidney substance becomes replaced by caseous material. Ulceration into the pelvis readily occurs, and the caseous areas undergo excavation, the pelvis becoming infected and ulcerated—*tuberculous pyelo-nephritis* (Fig. 434). Sometimes the disease is restricted to the region of the pelvis, which is extensively ulcerated and surrounded by a thick caseous layer. This is by some taken as indicating the result of an ascending infection, but manifestly the same result will be produced if the primary lesion occurs in the apex of a pyramid. The corresponding ureter usually shows marked tuberculous lesions. Its wall is thickened and nodular, its lining is ulcerated and its lumen may contain caseous pus.

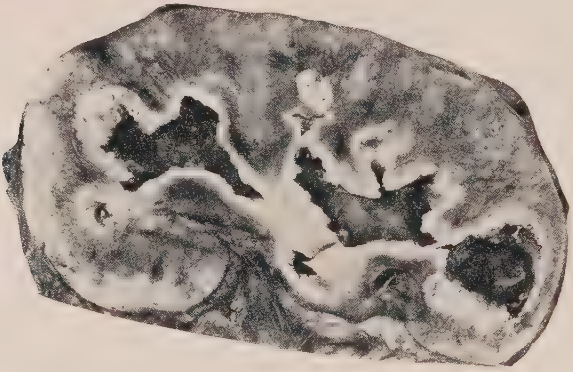

FIG. 434.—Caseating Tuberculosis of Kidney.

The lesions are especially around the pelvis—tuberculous pyelo-nephritis—and foci are present also in the kidney substance. × $\frac{5}{8}$.

When, as is not infrequently the case, there is obstruction below, considerable dilatation may occur. In some cases the ureter may become permanently obstructed at an early period of the disease, and this sometimes has a favourable effect in localising the infection. The affected kidney may be completely destroyed and then the caseous material may become inspissated and the seat of calcification. The capsule undergoes great thickening and the whole organ becomes shrunken, its substance being replaced by collections of thick putty-like substance (Fig. 435). Such a kidney, the site of effete tuberculosis, may be occasionally found *post mortem* where there was no suspicion that any disease of the kidney was present, and its occurrence shows the possibility of cure by surgical removal of an affected kidney when the disease is confined to it.

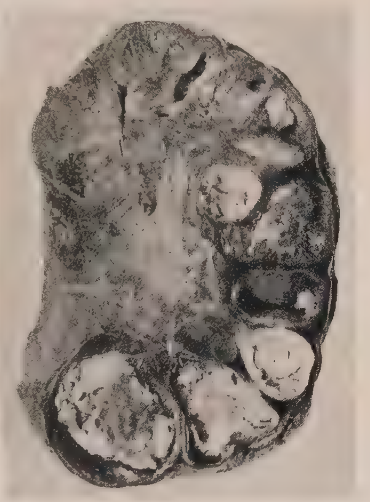

Fig. 435.—Old Tuberculosis of Kidney; its substance has been replaced by collections of caseous material enclosed by fibrous tissue. × $\frac{5}{8}$.

In tuberculous disease of the kidney the *urine* is usually turbid owing to the presence of pus, the cells of which are more or less degenerated, and sometimes the pus is abundant. Tubercle bacilli are usually to be found on microscopic examination, though sometimes they are very scanty and a long search may be necessary. It must be noted, however, that when the ureter of the affected kidney is blocked or obliterated, the discharge of material from the caseous areas is prevented, and no change may be present in the urine. In cases of tuberculous disease of the urinary tract, secondary infection with coliform or other organisms is not uncommon, and septic inflammation may be superadded; the condition is then greatly aggravated. Hæmaturia also is sometimes a distinct feature, especially in the early stages of the disease.

Syphilis. In the *congenital* form, spirochætes are to be found in the kidneys, and sometimes areas of leucocytic infiltration and connective tissue proliferation may be found. Such lesions, which are much less common than those in the liver and pancreas, may give rise to fibrosis at a later period. In the *acquired* form gummata are very rare, and although fibrotic lesions probably occur just as in other organs, we have no means of recognising them with certainty. Some writers believe that a form of granular contracted kidney may be produced by syphilis, and that the contracted amyloid kidney especially is of this nature. A form of nephritis accompanied by extensive lipoid degeneration of the tubules, has been described in the secondary stage, but it is not clear whether this lesion is due to syphilis or possibly to treatment with arsenical or mercurial compounds.

Actinomycosis rarely occurs in the kidneys ; the lesions are of the usual type.

Hæmaturia. This is so important a clinical sign that we may summarise with advantage the chief conditions which give rise to it, so far as the *kidneys* are concerned. In addition to actual laceration of the kidney by injury, hæmaturia is met with in certain groups of conditions.

(*a*) *Circulatory Disturbances.* Red corpuscles escape in the urine in chronic venous congestion, though usually the amount of blood is scanty ; more marked hæmaturia occurs in infarction and in the rare cases of thrombosis of the renal vein.

(*b*) *Inflammatory Conditions.* Red corpuscles are present in the urine in the various forms of acute nephritis, and sometimes the presence of blood is clearly recognisable on naked-eye examination. In cases where nephritis has existed for some time diffuse hæmorrhage may supervene—*hæmorrhagic nephritis*—especially when some infective condition is superadded ; it is often a marked feature in the nephritis secondary to subacute bacterial endocarditis (p. 668). Hæmaturia may be met with in suppurative disease, though it is usually slight ; it may, however, be a marked feature in cases of tuberculosis.

(*c*) *Tumour Growths.* Hæmaturia is often a prominent feature in cases of 'hypernephroma,' which is the commonest kidney tumour in the adult, and it may occur also in other forms of malignant disease. It is occasionally, though rarely, due to a simple growth, e.g. a papilloma of the pelvis ; and we have seen profuse hæmorrhage produced by a comparatively small angioma at the apex of a medullary pyramid.

(*d*) *Renal Calculus.* Hæmaturia, in varying degree, accompanies an attack of renal colic, due to the passage of a calculus along the ureter, but may occur apart from this condition.

These various conditions may, for practical purposes, be conveniently divided into those in which bleeding is unilateral and those in which it is bilateral, and it will be seen that such a division may readily be made. It should be added that in some cases severe unilateral bleeding occasionally takes place without the presence of any of the above conditions, and when the kidney is excised, no change except the presence of blood in some of the tubules is to be found. The nature of such cases is quite obscure. The lesions of the bladder, which may give rise to hæmaturia, are described below.

Sometimes the coloration of the urine is due to the presence of free hæmoglobin, and, as already explained, this depends on a previous lysis of the corpuscles in the circulating blood. The hæmoglobin becomes changed into methæmoglobin in varying degree. *Hœmoglobinuria* may be produced in this way by the action of various poisons, such as pyrogallic acid, arseniuretted hydrogen, nitrobenzine, and especially chlorate of potash, which is a not uncommon cause. It is occasionally observed after severe burns and in specific fevers and blood diseases, but its occurrence at such times is rare. Two important forms of the condition, namely, blackwater fever and paroxysmal hæmoglobinuria, have been already described (pp. 474, 487).

Congenital Cystic Kidneys

Occasionally both kidneys are greatly enlarged and occupied by numerous cysts of various sizes, whilst little kidney substance may be recognisable between the cysts. This condition occurs in the fœtus, and the kidneys may be so large as to interfere with parturition. Death may follow at an early period, but sometimes there is survival to late adult life, even where the lesion is of marked degree. Each kidney may weigh two pounds or even more (Fig. 436). The cysts may be of any size up to that of a small orange, and they contain usually serous fluid, though it may be mucoid, especially in the smaller cysts; the fluid is colourless, or may present varying degrees of brownish staining. Occasionally the cystic condition is practically restricted to one kidney. In adults, the presence of cystic kidneys is attended as a rule by a certain amount of hypertrophy of the heart, and death may occur from uræmia. The condition of cystic kidneys is apparently the result of disturbance of the normal development of the organs. A view which has received considerable support, is that it is due to imperfect fusion between the kidney tubules proper and the collecting tubules, which grow up from the extremity of the ureter to meet them. With regard to the cause of this disturbance, we have no definite knowledge. It is noteworthy, however, that the

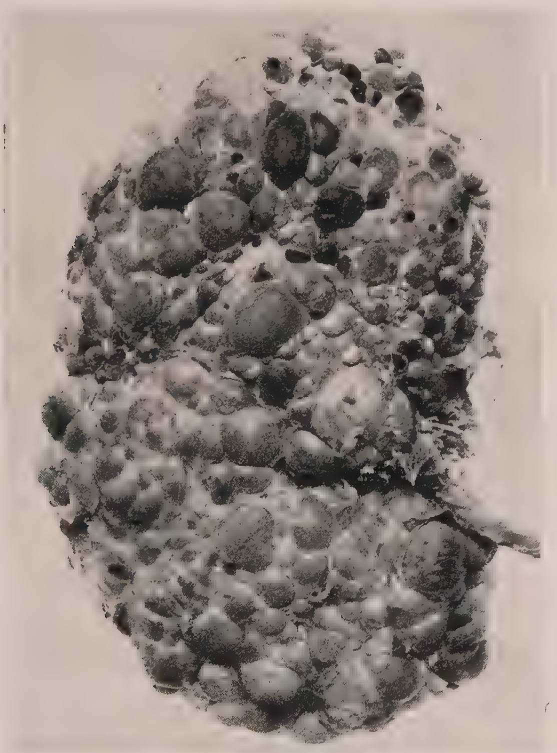

FIG. 436.—Surface view of congenital Cystic Kidney.
The kidney was 50 oz. in weight.

cystic state of the kidneys may be associated with a similar condition in the liver, and sometimes with other abnormalities. There is no evidence that obstruction of the tubules by a chronic inflammatory process is concerned in the production of cystic kidneys, as was at one time supposed. We have given an account of the disease in its extreme form, in which there is little kidney tissue to be seen ; but all degrees may be met with. In some cases a considerable number of isolated cysts are scattered in the kidney substance, or there may be a few cysts of larger size, and it is likely that the abnormality in development, which in its extreme form leads to cystic kidneys, is not uncommon in a minor degree.

Occasionally a single cyst is present and may reach such a size as to be palpable during life. The effects are merely mechanical.

The effects of cystic disease vary, of course, according to the amount of kidney substance which survives. In the severer forms of the lesion death occurs early as a rule, but we have seen cases of great cystic enlargement of the kidneys where life had been prolonged till after the age of forty. Death then may be due to the kidney condition, either from heart failure following hypertrophy or from uræmia. In a recent case with high blood pressure which we have seen, cerebral hæmorrhage led to the fatal result.

TUMOURS

Simple tumours of the kidney are comparatively rare, the commonest being the small *fibroma*, which is not infrequent in the medulla ; it rarely reaches a large size. *Adenoma* occasionally occurs, and a

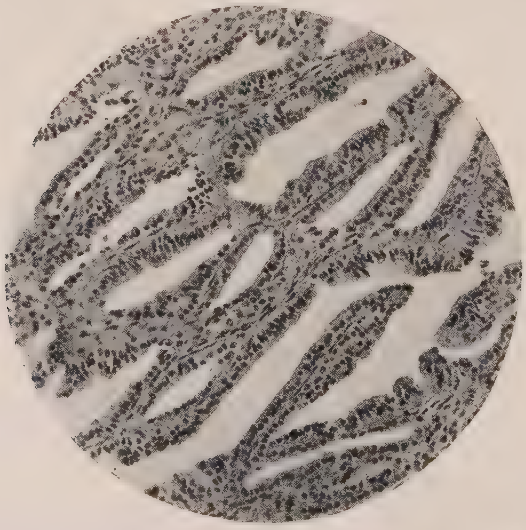

FIG. 437.—Papillo-adenoma of Kidney, showing the delicate Stroma and the characters of the Epithelium. × 140.

somewhat characteristic type is one with narrow bands of stroma and papilliform ingrowths (Fig. 437). Such a growth is usually quite simple, but we have seen malignant disease with metastases occur in connection with it. *Lipoma* is rare as a renal growth. In the pelvis *villous papilloma* is sometimes met with; it corresponds in structure to the common papilloma of the bladder. *Angioma* is another simple tumour occasionally met with. It may occur in the pyramids or just underneath the lining of the pelvis and, even when of small size, may lead to severe hæmaturia.

Of the *malignant growths*, two are of considerable importance, on account of their relative frequency. One occurs in the later years of life, being commoner in men, and is often called a *hypernephroma* or Grawitz's tumour. The other is a mixed tumour or nephroblastoma which is met with in children and is of congenital origin.

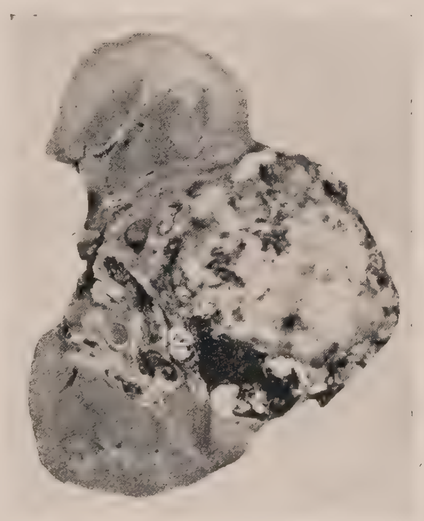
FIG. 438.—Hypernephroma growing from central part of Kidney.

Hypernephroma is often of considerable size and may occasionally form an enormous mass. It may occur in any part of the kidney and does not seem to be commoner at the upper pole than elsewhere. On section, there are usually large areas of dull yellowish tissue (presenting a certain resemblance to the adrenal cortex), interspersed with very vascular and hæmorrhagic areas, whilst there are also broad bands and patches of connective tissue somewhat mucoid or translucent in appearance (Fig. 438). Although a hypernephroma may be in the form of a localised nodule like a simple tumour, it shows distinctly malignant characters. It may grow into the branches of the renal vein and form thrombus-like masses within them; secondary growths may follow, especially in the lungs and bones. It may also burst through the capsule of the kidney or into the pelvis. Hæmaturia is of common occurrence and often a prominent symptom in cases of hypernephroma.

On MICROSCOPIC EXAMINATION, such a tumour has, as a rule, a distinctly acinous arrangement in many parts, the spaces being lined by tall columnar epithelial cells, which usually contain abundant droplets of doubly refracting fat and glycogen (Fig. 439); a papilliform type of growth also is sometimes present. Between the acini is a fine connective tissue stroma which bears numerous blood vessels.

In certain parts the arrangement of the epithelium is of the solid type ; it may become more irregular and aberrant types of cells occur.

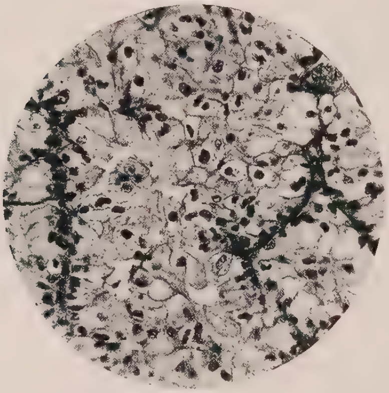

FIG. 439.—Section of Hypernephroma, showing the characteristic large Cells and delicate Vascular Stroma. × 200.

The nature of this growth has been the subject of much dispute. According to one view it arises from portions of displaced adrenal tissue, hence the name by which it usually goes. The other view is that it is really of kidney origin, and this seems to us to be better supported by the facts. The view as to adrenal origin was based on the supposed resemblance between its cells and those of the cortex of the adrenal, especially as regards the presence of myelin and glycogen and the general appearance of the growth. It has, of course, been long recognised that displaced portions of adrenal tissue are not uncommonly present on the surface of the kidney and even within the capsule. Against this view, however, is the fact that such adrenal rests occur in other parts, e.g. along the ureter, on the surface of the testicle, sometimes in hernial sacs in children ; whereas the 'hypernephroma' occurs only in the kidney, and a similar growth is not met with in the adrenal itself. Further, the tumour may arise in any part of the kidney, in the substance or on the surface, and, again, its cells are arranged so as to form distinct acini, an arrangement quite unlike the trabecular arrangement of the adrenal cortex. It may be mentioned also that in minute cysts in the kidney, which are not uncommon in the later years of life, the epithelium may come to contain myelin, and resemble that in the hypernephroma ; and it is quite likely that the tumour arises from such altered epithelium (Shaw Dunn).

It is possible that tumours under the title of hypernephroma are not all of the same nature, but the description given applies to the common type. We consider that the evidence is against its being of adrenal origin and that it should be regarded as a renal growth. Further, it is to be noted that the functional effects of tumours of the adrenal cortex (p. 962) are not found in cases of hypernephromata.

Nephroblastoma, which is really a mixed tumour, has the general appearances of a rapidly growing sarcoma. It may reach a large size and, though fairly well enclosed within the kidney capsule, rapidly invades the blood stream by the veins and so produces metastases, chiefly in the lungs. It is met with especially in the first three years of life. It is known also as 'embryoma,' 'mixed tumour' or 'Wilms' tumour' of the kidney. It is one of the commonest malignant growths in childhood.

Microscopically, the growth is in parts composed of a spindle-cell tissue, whilst in other areas there is formation of acinous and tubular structures, and apparent transitions may be seen between the spindle-cells and those of epithelial type (Fig. 440). There may be also imperfect formation of glomeruli. The growth was formerly often described as adeno-sarcoma, but there is little doubt that it is derived from the cells of the kidney rudiment, and that it represents imperfect formation of kidney structure. In some instances the growth has a more complicated structure, striped muscle fibres being present, and in such cases the tumour may have originated from a cell of the mesoderm before the differentiation of the myotomes. In view, however, of what has recently been established with regard to the part played by organisers in ontogeny, the explanation may be of another nature.

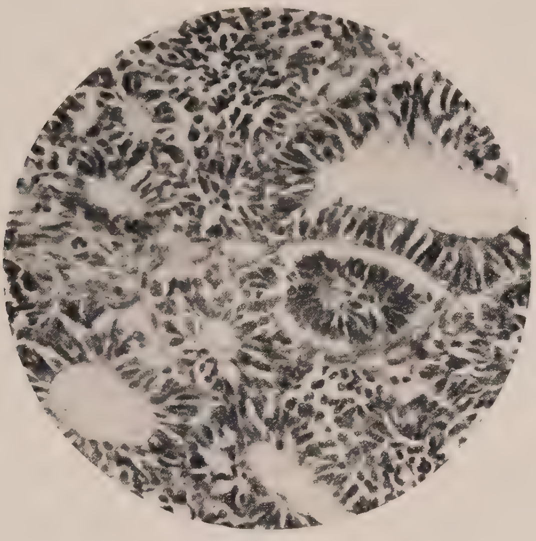

FIG. 440.—Nephroblastoma, showing cellular tissue with formation of acini by cells. × 250.

Carcinomata (usually adenocarcinomata) and *sarcomata* of ordinary types occasionally take origin in the kidney. Secondary growths occur, e.g. in oat-cell bronchial carcinoma, but, on the whole, are not common.

RENAL PELVES, URETERS, AND BLADDER

It is convenient to consider the lesions of these structures together, as they are so often involved in the same pathological process. Three main factors are concerned in the majority of these lesions, viz. (*a*) *obstruction to urinary flow*, (*b*) *infective inflammation*, and (*c*) the *formation of calculi*; and two or even all three of these may be present at the same time. We shall first consider the mechanical effects of obstruction.

Effects of Obstruction

Obstruction to outflow of urine from the bladder is practically confined to the male sex, and is commonly produced by stricture of the urethra or enlargement of the prostate; occasionally by severe phimosis, tumour, or calculus. The chief effect on the bladder is the production of hypertrophy and dilatation, and the proportion of these varies much in different cases. Sometimes the outstanding feature is hypertrophy; the muscular part of the wall is thickened and the bands of muscle, which have a sort of reticulated arrangement under the mucosa, become enlarged and form prominent ridges or bands with depressions between. Occasionally one of these depressions may become enlarged and form a projecting diverticulum which may reach a considerable size. When infection occurs, as is so often the case, a large accumulation of purulent material may form in such a diverticulum, and occasionally ulceration and even perforation may follow. Obstruction to outflow from the bladder ultimately leads to accumulation of urine also in the ureters and pelves of the kidneys. The former may undergo considerable dilatation and their walls become somewhat thickened, and the pelves also become enlarged, so that there is a condition of double hydronephrosis. The dilatation is sometimes more marked on one side than on the other.

Hydronephrosis. This means a dilatation of the renal pelvis and may occur on one side or both sides. In addition to obstruction at the outlet of the bladder, as just described, *double* hydronephrosis is occasionally produced by a growth, e.g. of the bladder or female pelvic organs, pressing on or implicating the lower ends of the ureters. It may be mentioned here that dilatation of the ureters and hydronephrosis are occasionally due to congenital abnormality in the posterior urethra, the mucosa of which forms valve-like folds. In all these conditions of double hydronephrosis the dilatation of the ureters and pelves is usually of moderate degree. The most striking degree of hydronephrosis occurs when the obstruction is *unilateral*, and this may be due to various causes. It may be due to a calculus, which is often impacted at the upper end of the ureter, though sometimes at a lower level, especially at the entrance to the bladder. It may be produced also by a cicatrix, which sometimes follows ulceration due to the passage of a stone; also by pressure of a growth from outside, rarely by a tumour within the pelvis. It occasionally results when the ureter is attached at an abnormally high level to the pelvis, so that it leaves it at an acute angle, and a valve-like obstruction results. Such a condition may be attended by intermittent accumulation of urine, and ultimately marked hydronephrosis may develop. Hydronephrosis may result when the ureter has been bent over the renal artery in an abnormal position, and in a recent series of cases we have found this to be not infrequent. The condition is well shown in Fig. 441. It has also been occasionally, though rarely, met with when the kidney has been in an abnormal position. In some cases no cause of the hydronephrosis is discoverable.

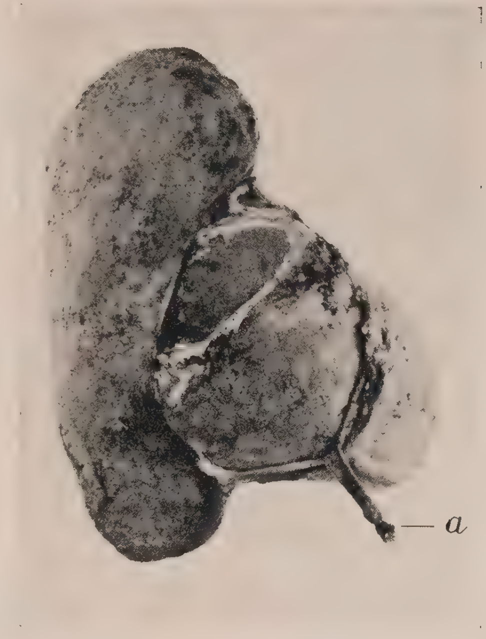

FIG. 441.—Hydronephrosis showing ureter (*a*) hooked round renal artery. × ½.

The effects of obstruction vary greatly. Sometimes a calculus may be firmly impacted, and there may be moderate distension of the pelvis (Fig. 442), or the whole pelvis may be distended by a branching calculus to which the kidney substance is closely applied. In such cases, fibrosis and atrophy of the kidney follow. In other cases again, the distension is very great, and the dilated pelvis may reach the size of a child's head. As the distension occurs, the calyces become flattened out, the kidney substance becomes stretched over the dilated pelvis, and ultimately may form a mere rind; the surface of the kidney usually comes to have a lobulated appearance. Atrophy of the kidney substance may be regular or irregular, so that parts of considerable thickness may be left while the rest is much thinned; the latter result apparently depends on the way in which the vascular supply is interfered with. Sometimes, however, the dilatation is mainly in the form of a sac projecting outwards and there is little effect on the kidney substance—the extra-renal as contrasted with the renal type of hydronephrosis.

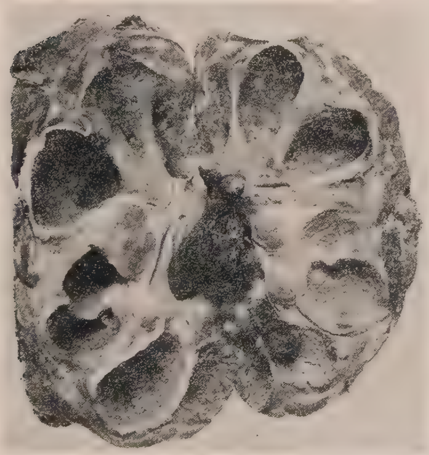

FIG. 442.—Impacted branched Calculus in Renal Pelvis with resulting Hydronephrosis and great fibrous thickening. × ½.

The experimental results of obstruction of a ureter vary somewhat, but, as a rule, it has been found that excretion of urine is soon brought to a standstill and comparatively little dilatation follows, and the explanation generally given of severe hydronephrosis in the human subject is, that it occurs when the obstruction is intermittent. When the obstruction is relieved, e.g. by a calculus changing its position, there results a great flow of urine, and if the obstruction becomes partial again, this will lead to further expansion. It is easy to understand, therefore, how such an occurrence, often repeated, may bring about great distension. It must be understood, however, that not infrequently great hydronephrosis is associated with complete obstruction and, it may be, obliteration of the ureter; in such a case obstruction may have been intermittent at some time. When the kidney becomes stretched and thinned, the tubules, and ultimately the glomeruli, become atrophied, and there ensues general overgrowth of the connective tissue. The contents of a dilated pelvis are, of course, at first urine; but, as the condition becomes chronic, the urinary constituents disappear, whilst proteins are added to the fluid by transudation from the wall of the sac.

Inflammatory Conditions

It is important to distinguish those which are superadded to obstruction and those which occur apart from it.

(A) **Inflammation without Obstruction.** This is produced chiefly by bacilli of the coli group and varies greatly in severity. In the female, infection along the short urethra is comparatively common, both in children and in adults, but we are doubtful if this occurs in the male, apart from gonorrhœal cases or the passage of a catheter. Blood-borne infection, however, is the common occurrence and in the great majority of instances the primary site of lesion is the renal pelvis or the substance of the kidney. In some cases, cystitis is the primary lesion, and from this there may be an ascending infection to the pelvis of the kidney, but we believe that this is exceptional, unless there is at the same time some obstruction leading to dilatation of a ureter.

Acute pyelitis has long been recognised as a condition with distinct features. It is common in children in the early years of life although it may occur at any age; it has also relation to pregnancy. It is as a rule attended by marked pyrexia and is commonly due to coliform organisms; and when this is the case it is often very amenable to treatment which renders the urine alkaline. More recently it has come to be recognised that in the great majority of cases the kidney substance is involved, is then the condition known as pyelonephritis. Blacklock, for example, has found that in children pyelitis with pyuria is usually secondary to focal inflammations in the kidney substance which may be suppurative. In some cases there may be multiple foci of suppuration, or involvement of the kidney may be of a more diffuse inflammatory character. Such changes are ordinarily followed by overgrowth of connective tissue which may be patchy or more general and a condition of chronic pyelonephritis may thus result.

Chronic pyelonephritis is much commoner than was formerly supposed. It may lead to a general fibrosis with shrinkage of the kidney substance and granularity of the surface ; in fact to a type of granular contracted kidney. Or more irregular scarring may result. Both kidneys may be affected, one often more than the other, or the condition may be unilateral. The pelves of the affected organs are often dilated, as are sometimes the ureters. The lesion is essentially a chronic interstitial one which affects secondarily both glomeruli and tubules in an irregular way.

The importance of such lesions is the serious functional results which may follow. Hypertension appears and this may be of marked degree and assume the characters of the malignant type with the usual changes in the arterial system. Involvement of glomeruli and tubules leads to urea retention and the patient may die from uræmia. In fact, we may say that a type of malignant nephrosclerosis may be the result of damage done to the kidney by pyelonephritis.

The urinary tract is not infrequently infected from the kidney by the typhoid bacillus in the course of enteric fever. Usually only a mild catarrhal inflammation is the result, and the condition may be almost a pure bacilluria. The bacilli may persist for an indefinite period of time, the patient being then spoken of as a ‘ urinary carrier ’ (p. 179). In some cases of coli infection also, there may be comparatively little inflammatory reaction. Cystitis may be produced by the gonococcus in cases of gonorrhœa, and has usually the features of a purulent catarrh. It is to be noted that bacilli of the coli group and the gonococcus do not render the urine alkaline.

Inflammation with Obstruction. When cystitis follows an obstructive lesion the effects are of a more serious kind. Here also infection may be by the blood stream, usually by organisms of the coli group ; but in many cases it is the result of the passage of a catheter, for example, in cases of chronic stricture, enlarged prostate, also in paraplegia with paralytic distension of the bladder. A variety of organisms—micrococci, bacilli of the coli and proteus groups, etc., and even moulds—may then be present. Alkaline decomposition of the urine, which may be due to various bacteria, often results, and may lead to a precipitation of triple phosphates and urate of ammonium.

All these inflammatory conditions present the usual features, and may be attended by hæmaturia in varying degree. As regards the anatomical changes in cystitis, these are usually classified as (*a*) catarrhal, (*b*) purulent, and (*c*) pseudo-membranous. In the last mentioned, which is chiefly met with when there is hypertrophy of the bladder, there occurs superficial necrosis of the mucosa with fibrinous exudate, especially over the muscular ridges. In some cases even a gangrenous condition may be superadded, and the lining of the viscus becomes separated in decomposing shreds. The most severe effects are usually met with where there is alkaline decomposition of the urine. Hæmorrhages into the mucosa are common, and these may become of a greenish and almost black colour, whilst the surface is covered with pus and often considerable deposit of phosphates. Such an infection may ascend the dilated ureters, and produce a pyelitis of corresponding character, and the pelvis may become ulcerated or filled with an accumulation of pus—*pyonephrosis*. Here also secondary deposit of phosphates may occur. Ultimately, the infection may extend to the kidneys and give rise to abscesses in their substance—the 'surgical kidney' (p. 690). Often only one pelvis is affected in this way, but both pelves may be involved, although in an unequal degree.

Malakoplakia. This is a rare condition met with in some cases of chronic cystitis, and is characterised by the formation of numerous soft rounded elevations or plaques in the bladder wall, in size up to that of a bean. They have a pale, sometimes yellowish appearance surrounded by vascular areas, tend to be ulcerated on the surface and invaded by bacteria, and are essentially composed of cellular granulation tissue in which there are numerous large cells with peculiar features. These cells contain droplets of various kinds and small hyaline spheres with concentric marking, also inclusions of red corpuscles and leucocytes. The rounded structures may become free by disintegration of the cells. Lime salts may be deposited in them and they have also an affinity for iron, as can be shown by the usual tests. The lesion is of the nature of a granuloma, but whether it is produced by coliform and other organisms, or by some rare specific organism, has not been determined.

Tuberculosis. Tuberculous disease of the bladder is, as a rule, the result of direct infection of its mucosa by the bacilli in the urine, in a manner corresponding to what is seen in the case of the intestine (p. 564) It occurs most frequently in cases of renal tuberculosis, though also in tuberculosis of the genital tract. The bacilli invade the mucosa and give rise to tubercles which then undergo ulceration. In this way, multiple small ulcers are formed, especially at the base of the bladder, and sometimes the orifices of the ureters are specially involved. The ulcers increase in size and form large areas by confluence. Sometimes there is a considerable amount of caseous thickening of the lining. Secondary invasion by other organisms sometimes occurs, and more acute inflammatory change, which may be attended by ammoniacal decomposition of the urine, is superadded.

Bilharziasis. The bladder is the most frequent site of lesions in this condition, which is produced by the *Schistosoma hæmatobium* ; and in some countries, notably in Egypt, the disease is very common. The adult parasites lie in the vesical veins, and the eggs laid by the female pass into the surrounding tissues, where they are to be seen in large numbers. The irritation produced results in the formation of abundant vascular granulation tissue which causes great thickening of the mucosa and submucosa. Nodular upgrowths also form, and the interior of the bladder may be beset with rounded and somewhat pedunculated vascular projections, which tend to become ulcerated. Hæmaturia is a common feature and the ova are readily found in the urine. Septic inflammations may become superadded, and an important fact is that carcinoma develops in a fairly large proportion of cases. Bilharzial lesions are sometimes met with also in the ureters and renal pelves.

The *Schistosoma hæmatobium* is a diœcious trematode. The adult male is about 13 mm. in length, the female about 20 mm.; the latter is more filiform and lies enclosed in the gynæcophoric canal of the male. The eggs are oval in form, about 130 μ in length, and the shell has a distinct terminal spine; the embryo is visible within. When the urine becomes diluted on being mixed with water, the investing shell swells and bursts and a ciliated embryo or miracidium escapes. This has been shown by Leiper to penetrate the body of certain fresh-water snails (*Bullinus contortus* and *Bullinus dybowski*) within which it passes to the liver and then develops a sporocyst. A redia stage is then passed through and ultimately free-swimming cercariæ are developed. The cercariæ gain entrance from water to the human subject, chiefly through the skin but also through the mucous membrane of the mouth and pharynx. They reach the liver and attain sexual maturity within the portal vessels. The young adults then pass against the blood stream to the portal radicles, especially those of the inferior mesenteric vein, and thence they reach the vesical plexus, where they settle as described above. Occasionally the parasite remains in the liver and the eggs are discharged into the periportal connective tissue and give rise to a form of cirrhosis (p. 608) It had previously been noted that in bilharzial lesions two types of ova occurred, one with a terminal spine and one with a lateral spine, the latter being met with especially in intestinal lesions; and it was believed that these represented two species of parasites (Fig. 363). This was definitely proved to be the case by Leiper, who worked out the histories of the two species now known as *Sch. hæmatobium* and *Sch. mansoni.* He showed that, in the case of the latter, which produces ova with lateral spines, the intermediate host is another species of snail, namely, the *Planorbis boissyi*, within which the parasite passes through stages of development corresponding to those just described. The *Sch. mansoni* is the cause of the intestinal lesions (p. 568) which are of nature corresponding to those of the bladder.

CALCULI

Urinary calculi are formed by a separating out in crystalline or granular form of the constituents of the urine, a small amount of organic material also being incorporated. The process may start around some organic nucleus, or simply may be the result of saturation; in any case, excess of a particular substance is the important factor as a rule. Calculi may be met with in the pelvis—*renal calculi*, or in the bladder—*vesical calculi*, although some of the latter originate in the kidneys.

Renal Calculi. These are usually composed of a mixture of uric acid and urates—'uric acid stones'—occasionally of calcium oxalate. There is evidence that in the case of both varieties minute concretions may form first in the collecting tubules of the kidney and then pass into the pelvis where further increase in size takes place. Within the pelvis multiple small stones may form, especially when it is dilated, and occasionally they may be in enormous numbers; or on the other hand, a calculus may gradually grow by further deposit and come to form a branching mass filling the pelvis (Fig. 443). The amount of hydronephrosis produced varies greatly as has already been described. A small calculus often passes along the ureter to the bladder, giving rise to renal colic, which is associated with hæmaturia, etc. It may be arrested for a time by the constriction of the ureter at its entrance to the bladder. On the other hand, the calculus may

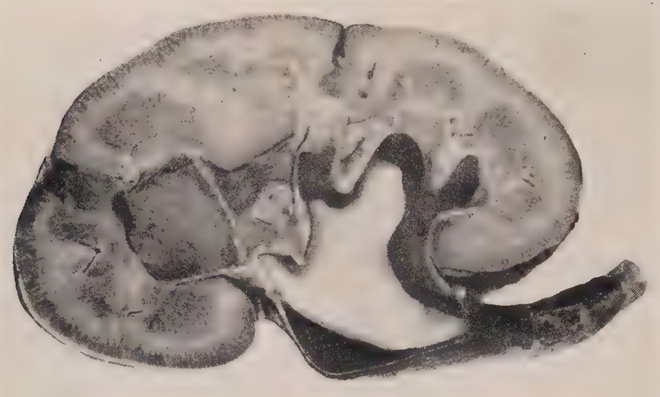

Fig. 443.—Large Renal Calculus, forming a cast of lower part of Pelvis and obstructing the Ureter. × $\frac{2}{3}$.

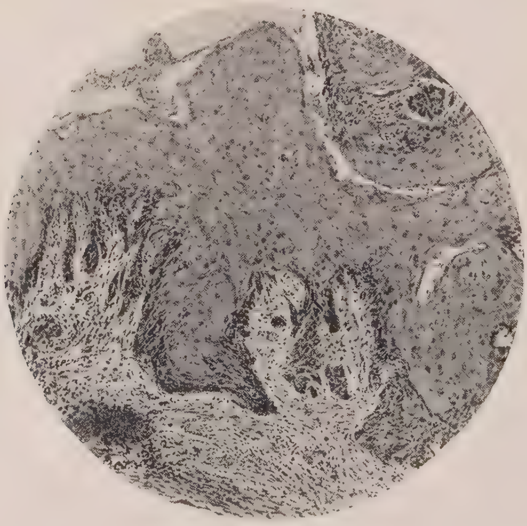

Fig. 444.—Section of Lining of Renal Pelvis in a case of Calculus, showing Metaplasia of Epithelium to the stratified squamous type and commencing Epithelioma. × 65.

be impacted, usually in the upper end of the ureter, and produce hydronephrosis as already described, and when the obstruction is of the intermittent variety, the hydronephrosis may reach a large size. When there is infective inflammation accompanied by ammoniacal decomposition of the urine, calculi or mortar-like material composed of phosphates often form in the inflamed pelvis, the condition being attended by suppuration, ulceration, etc. A calculus in the renal pelvis, especially when it is movable, may give rise to metaplasia of the lining of the pelvis into stratified squamous epithelium. As a further result of the irritation epithelioma has occasionally been found to arise, as is illustrated in Fig. 444.

Vesical Calculi. These may be single and reach a great size, or they may be multiple, sometimes numerous and like coarse sand. In some cases calculi form in the renal pelvis, especially uric-acid calculi, and then pass to the bladder, where they increase in size ; in other cases they are formed locally. The larger calculi present great variations in composition and structure, but as a rule there is a nucleus or centre surrounded by concentric laminæ. According to Kleinschmidt, the nucleus or primary stone is formed by the separating out of the particular substance from a saturated solution in the urine, and has the same composition throughout. The *primary stones* formed in this way are composed of urates and uric acid (by far the commonest variety), less frequently of calcium oxalate or calcium phosphate, rarely of cystin or xanthin. The primary urate stone, seldom larger than a small pea, and often formed first in the renal pelvis, is of rounded form, hard consistence and brownish colour. The primary oxalate stone is very small and hard with irregular outline, and is often of dark brown colour from altered blood pigment. It is to be noted that the large oxalate calculus known as a ‘ mulberry calculus,’ a round hard stone with nodular surface (Fig. 445), is usually a composite stone with a varying proportion of urates and oxalates in the outer layers. Primary phosphatic stones are of whitish colour, often friable, but sometimes hard. They are met with in experimental hypervitaminosis D (p. 829). Any of these primary stones, like other foreign bodies, may have *secondary* deposits formed on their surface, and thus secondary or laminated calculi arise, these often reaching a large size. The particular substance secondarily deposited, which need not be in a saturated state in the urine, depends not only on the composition of the urine but also on its reaction, urates especially being deposited when the reaction is acid (Fig. 445), phosphates when it is alkaline. As the state of the urine varies from time to time, the great variations in the composition of stones can be readily understood. Thus a primary urate stone may be surrounded by laminæ of mixed urates and oxalates, or of phosphates, etc. Vesical calculi sometimes reach a great size. For example, we have in our collection a large oval stone measuring three inches in length and weighing ten and a half ounces ; it was removed from a native of India. The central part is a laminated urate stone and has a thick phosphatic mantle.

These two kinds of stones, primary, and secondary or laminated, may form without the presence of bacterial infection or inflammation, and lead to mechanical effects—pain and irritation with hæmaturia, intermittent obstruction, damage to the bladder mucosa with ulceration, etc. When, however, there is secondary bacterial invasion, and ammoniacal decomposition of the urine occurs, then triple phosphates and ammonium urate separate out, often in large amount, and form a further deposit on calculi already formed. Deposits of these substances may occur also in cases of septic cystitis (p. 702) apart from the previous occurrence of calculi, and form primary inflammatory calculi or irregular cretaceous deposits.

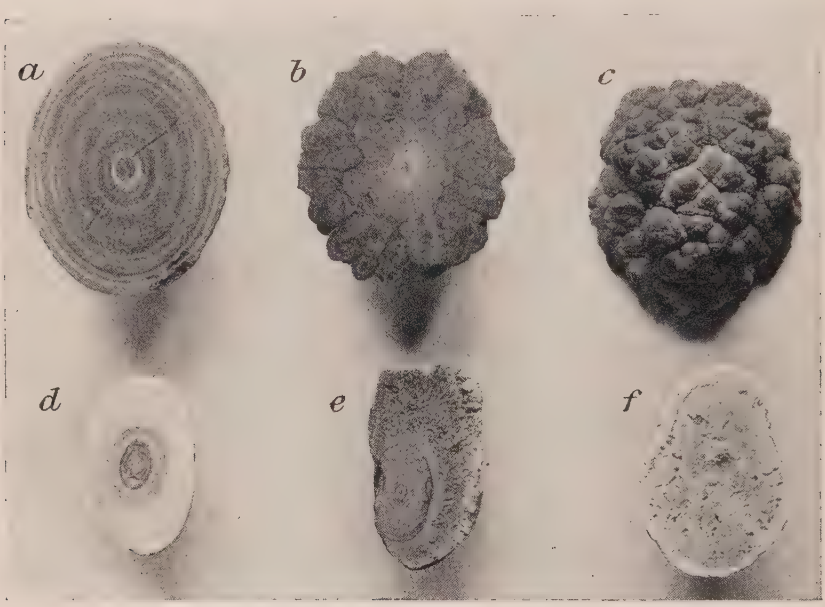

FIG. 445.—Types of Vesical Calculi.

a, uric-acid calculus, showing characteristic lamination around the primary calculus; *b*, oxalate or mulberry calculus seen on section, and *c*, surface view of the same; *d*, laminated phosphate calculus around a central nucleus; *e*, small laminated phosphatic calculus with irregular incrustation deposit on the surface; *f*, non-laminated phosphatic calculus of incrustation type. × $\frac{3}{4}$.

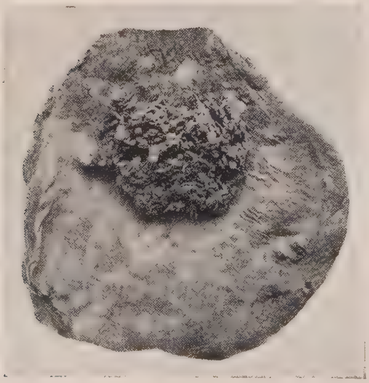

FIG. 446.—Papilloma of Bladder. × $\frac{4}{5}$.

TUMOURS

With the exception of the villous papilloma, simple growths of the bladder are very rare. *Myxoma*, *leiomyoma* and *rhabdomyoma* have occasionally been met with, and the last mentioned may form a huge lobulated mass. *Villous papilloma*, which is a fairly common growth, is met with especially in the region of the trigone ; it is usually single but sometimes multiple. The growth, as already described (p. 220), consists of delicate branching vascular processes of connective tissue, covered by several layers of cells of the transitional type. It may have a narrow base of attachment and project freely into the bladder and is often of simple character ; on the other hand, the base may be wider (Fig. 446), and then the growth is apt to develop malignant characters ; in fact, all transitions to carcinoma are met with. Villous papilloma occasionally occurs in the renal pelvis. Cancer and other forms of tumours are very rare in that situation.

Of the malignant growths, by far the commonest is the papillary form of *carcinoma* usually met with at the base of the bladder. It is a somewhat soft growth with villous surface at first, but tends to undergo necrotic softening and ulceration, and causes local destructive changes, sometimes with perforation; metastases are rare, however. On microscopic examination of such a growth some of the villi may show the structure of simple papilloma, others show aberrant types of epithelium, whilst in the deeper parts broad masses of similar cells can be seen infiltrating the muscular tissue. In the most malignant forms the cells are arranged in infiltrating masses without definite arrangement and show aberrations in type, numerous mitoses, etc. Other forms of cancer, including squamous epithelioma, are occasionally met with. The origin of cancer of the bladder is sometimes related to chronic irritation; this is well illustrated in the case of bilharzial disease (p. 704). In this connection it is interesting to note that bladder tumours, both papilloma and carcinoma, have been produced in dogs by beta-naphthylamine (Huepper and others). In recent years a number of cases have been observed in Germany where malignant disease of the bladder has occurred in aniline-workers. *Sarcomata* of the bladder are very rare. *Rhabdomyoma* may be mentioned as another growth of rare occurrence.

CONGENITAL ABNORMALITIES OF THE URINARY SYSTEM

In the case of the *kidneys* these are of comparatively frequent occurrence but are rarely of importance, if we except the congenital cystic condition already described (p. 694). Occasionally one kidney, usually the left, is absent—*agenesia*—and there is generally an absence of the ureter also. In such cases, the surviving kidney undergoes compensatory hypertrophy, and its weight may sometimes equal that of the two kidneys. *Hypoplasia* or imperfect development of one kidney is also met with, the kidney being sometimes an irregular atrophic structure around the upper end of its ureter. Here, also, hypertrophy of the other kidney occurs. Hypoplasia of both kidneys may occur to such a degree as to be incompatible with life ; minor degrees of the condition may possibly lead to renal dwarfism. Sometimes the two kidneys are fused, and this most frequently occurs at the lower pole, so that what is known as the '*horse-shoe kidney*' results; sometimes the union is merely by a fibrous band. In such case, the pelves are directed somewhat forward and the two ureters pass in front of the connecting bridge. In rarer forms the fusion of the kidneys is more complete and an oval or somewhat irregular mass results, which varies in position. Occasionally a kidney, more rarely both kidneys, may be displaced, the condition being known as *dystopia.* The displaced kidney is usually low down in front of the sacrum or in the pelvis; its ureter is correspondingly short and the arterial blood supply comes from the lower end of the aorta or an adjacent large branch. It is to be noted that in the various conditions of absence or displacement, the position of the adrenals is usually quite normal. The kidney is originally composed of lobules and ordinarily the fusion is complete, though the composite character of the kidney is seen in its interior. Sometimes slight grooves on the surface mark the original lobules and the term *fœtal lobulation* is applied; the condition, which is of no importance, is not to be mistaken for a pathological change. It is more marked in the child than in the adult.

Abnormalities affecting the *pelves* and *ureters* are met with sometimes. The ureter may be double in its upper part, the two parts then uniting, or in its whole length; and in either case, a partial doubling of the pelvis is usually present. When the doubling is complete, the ureter from the upper part of the kidney opens separately, more medially and lower down in the bladder, sometimes into the urethra or a vesicula seminalis. Such a condition may be present on one side or on both sides. Congenital narrowing or *atresia* of a ureter may give rise to dilatation of the part above and of the pelvis; an abnormally high origin of the ureter from the pelvis also may lead to hydronephrosis (p. 700).

The most important abnormality of the *bladder* is a defect of its anterior wall, accompanied by a corresponding medial defect of the abdominal wall, the condition being known as *extroversion* of the bladder. The posterior wall of the bladder is thus exposed, and appears as an area of vascular mucous membrane, showing folds and elevations on which the ureters open. The epithelium of the exposed mucosa undergoes metaplastic alteration, in part into squamous epithelium and in part into a columnar epithelium, resembling that of the intestine. In the male, the urethra remains open on its dorsal aspect, the condition being known as *epispadias*; in the female there is usually a split clitoris. Deficiency of the symphysis pubis also is present as a rule, though this may occur apart from extroversion of the bladder.

CHAPTER XVI

THE NERVOUS SYSTEM[1]

THE BRAIN

Introductory. If we consider the morbid changes of the nervous system as a whole, we find that some correspond in their nature with those observed in other organs—for example, those produced by infections, arterial disease, and tumour growth. Such lesions, in fact, account for a pretty large proportion of cases of nervous disease met with clinically. In another group of cases the primary change is in the neurons, sometimes in their axons, and is of degenerative nature; and whilst it is often manifestly the result of the action of poisons or toxins, the source and nature of these are in many instances quite obscure. Lastly, in another group of affections often spoken of as *functional*, no structural changes to explain satisfactorily the symptoms can be found, and the etiology is in the main unknown. Acute insanity and various mental disturbances are prominent examples of this last group. The brain and spinal cord will be considered separately, but in connection with a few subjects such as meningitis, tumours, etc., they will be treated together. This arrangement is merely one of convenience.

In connection with the pathological changes in the brain we may refer to some anatomical facts of importance. In the first place the arrangement of the membranes and the distribution of the cerebro-spinal fluid are intimately concerned with the spread of pathological processes. The dura mater, so far as disease is concerned, is to be regarded as a structure quite separate from the pia-arachnoid. It acts as a periosteum to the cranial bones, it is rarely the seat of infection by the blood stream, and its diseases are mainly of surgical nature. The pia and arachnoid may be considered really as parts of one membrane. The arachnoid forms a continuous membrane in contact with the dura, while the pia follows the windings of the convolutions, and the space between them, known as the subarachnoid space, is broken up by trabeculæ of connective tissue into a series of intercommunicating spaces, filled with cerebro-spinal fluid. This subarachnoid space or meshwork of the arachnoid in certain places is of considerable size, forming the cisterna magna and the cisterns at the base of the brain; apart from these it is broadest in the sulci, and there the main vessels run, the veins superficially, the arteries at a deeper level. The arterial branches ultimately break up in the pia into minute twigs from which the small nutrient vessels pass into the grey matter. At the perforated spots at the base of the brain there enter the nutrient arteries of the basal ganglia and other deep structures; these are long in proportion to their thickness and in certain conditions are liable to rupture (p. 724).

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[1] For a fuller account of the subject the student is referred to the *Pathology of the Nervous System*, by Buzzard and Greenfield, London, 1921; *Cytology and Pathology of the Nervous System*, edited by Wilder Penfield, New York, 1932; and *Pathology of the Nervous System*, by J. Henry Biggart, Edinburgh, 1936.

As an artery penetrates the brain substance, it carries with it a thin layer of the connective tissue of the pia, and the space, or rather potential space, between this tissue and the artery wall, known as the *Virchow-Robin space* or *perivascular space*, is thus continuous with the subarachnoid space (Fig. 447). This arrangement continues down to the ultimate terminations of the arterioles. The prolongation of the pia around the vessels, of course, lies next the grey matter, and a thin space between the two, often seen in sections, is known as His's space. It is doubtful, however, whether any real space exists in this position, although sometimes effused blood may be seen between the ordinary connective tissue and the neuroglia of the grey matter. These arrangements are of importance in connection with the spread of pathological processes. Thus organisms and their toxins readily diffuse in the subarachnoid space or meshwork of the arachnoid, and inflammatory exudate occurs around the blood vessels in this position. The inflammatory process may thence spread around the nutrient blood vessels passing into the brain substance, which are often seen to be surrounded with collections of leucocytes in the perivascular space. This space also forms a path by which products of degeneration are removed from the brain substance.

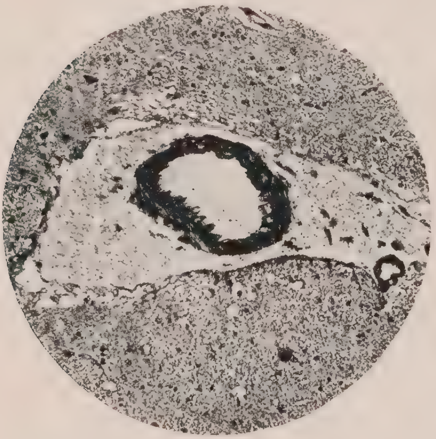

FIG. 447.—Hæmorrhage into Virchow-Robin space.

The blood shows the relation of the small artery to the brain tissue. (A. C. L.) × 100.

The communications between the subarachnoid space and the ventricular system are likewise of importance. These are the foramina in the roof of the fourth ventricle which readily allow the passage of fluid. Thus, for example, when hæmorrhage occurs into the ventricles and the blood makes its way down the aqueduct into the fourth ventricle, it then passes into the subarachnoid space and may spread widely at the base of the brain. It may also pass for a considerable distance over the surface of the cord. In a similar way an inflammatory process may spread from the ventricles to the meninges, or in the reverse direction. The cerebro-spinal fluid has a definite circulation and this is all-important in connection with the various pathological states. This subject, however, will be dealt with in greater detail in connection with obstruction to the circulation of the fluid (p. 733).

The condition of the cerebro-spinal fluid,[1] obtained ordinarily by lumbar puncture, often gives valuable information in diseases of the nervous system. The changes met with are partly in the cells of the fluid and partly in its chemical composition; they are manifold in character and only the most important of them can be given in the accounts which follow. It may be well to recall, however, that the cells normally present are almost entirely lymphocytes, the number of these being only about 4 per c.mm. In disease the number of these cells often rises greatly and other cells, especially polymorpho-nuclears, may be present. The normal cerebro-spinal fluid is quite clear and colourless, does not coagulate and its specific gravity is 1,006. It contains only a small amount of protein—about 0·02 per cent., and also about 0·05 per cent. of glucose. The chief salt is sodium chloride which occurs approximately in a percentage of 0·75.[1]

The Connective Tissues of the Brain. The existence of two kinds of connective tissue in the brain—neuroglia and ordinary connective tissue—is to be borne in mind, as both undergo reactive changes. The latter, of course, exists in the membranes and extends inwards along the blood vessels, as already explained, whilst elsewhere the neuroglia forms the supporting substance. In its general reactions neuroglia resembles ordinary connective tissue; its cells become enlarged and proliferate, and then produce glial fibres in increased amount. It must be recognised, however, that the process of growth is slower than in the case of the ordinary connective tissue. The neuroglial reaction is seen when there is any damage to the brain substance proper. Thus it occurs in association with degeneration of the nervous elements, as a sequel to any acute inflammatory change affecting the nervous matter, and around any focus of chronic irritation. The growth of ordinary connective tissue, on the other hand, is seen in grosser lesions where the blood vessels and their sheaths are involved. For instance, when suppuration occurs in the brain substance, there is an abundant growth of this connective tissue along with new formation of blood vessels, and in this way the encapsulating membrane of the abscess cavity is produced. In such a case, neuroglial overgrowth and condensation occur also, but this is a slower process and extends outside the granulation tissue enclosing the abscess. Apart from such gross destructive lesions, however, the reactive changes in the brain and spinal cord are chiefly on the part of the neuroglia.

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[1] For details, see *The Cerebro-spinal Fluid in Clinical Diagnosis*, by J. G. Greenfield and E. A. Carmichael, London, 1925.

It has long been recognised that the cells of the neuroglia are of two main types, namely the characteristic branching cells or astrocytes, and smaller cells of somewhat indeterminate character. Recent observations, especially those of Hortega and other workers of the Spanish school, show that the latter cells are of two distinct kinds, viz. (*a*) small cells of epiblastic origin (like the astrocytes), now known as *oligodendroglia* on account of their possessing a few small processes, and (*b*) small cells of mesoblastic origin called *microglia* or preferably *mesoglia*. The large-celled glia now known as *astroglia*, *macroglia* or simply as neuroglia, may be regarded as constituting the supporting tissue of the central nervous system, and the gliosis common in so many pathological states is the result of the proliferation of its cells. The mesoglia also plays an important part in disease ; its cells, ordinarily inconspicuous, become enlarged and spherical ; they are then actively amœboid and phagocytic, and play an important part in removing products of degeneration. They are often seen to be laden with fatty and lipoid globules and are known as ‘ compound granular corpuscles ’ (Fig. 455). (Cells of the latter class may, however, arise also from the adventitial cells or histiocytes around blood vessels.) After they have taken up the products of degeneration they may pass into the perivascular sheaths of the small vessels where they may be found in large numbers. The mesoglial cells may be regarded as the homologues of the histiocytes of the ordinary connective tissue (p. 83) : there is no evidence that they form glial fibres. Some facts are given below with regard to the oligodendroglia, but less is known as to its functions in pathological states.

It may be added that tumours, as will be described, usually arise from macroglia, though occasionally from oligodendroglia. Tumours of the mesoglia are, however, unknown. As the term ‘ neuroglia ’ has been so long used to indicate the formative connective tissue, we shall use it in the following account in this sense.

Leucocytes are extremely scanty in the substance of the brain and spinal cord under normal conditions, or are practically absent, but may occur in large numbers when pathological changes are present. In certain conditions damaged nerve cells may be seen in process of absorption by ‘ neuronophages,’ as they are called ; both mesoglial cells and leucocytes exert this phagocytic action. We give some further facts with regard to the glial cells.

The *astrocytes* are stellate cells with numerous fine branching processes. Protoplasmic astrocytes and fibrillary astrocytes may be distinguished ; the latter have fibres in their protoplasm, which run from cell to cell, and their processes are longer and straighter. In normal conditions the protoplasmic astrocytes are found mainly in the grey matter, the fibrous astrocytes in the white matter and subpial glial layer. Both forms are attached to the walls of capillaries and other small vessels by one or more vascular processes with swellings at their ends, the so-called ‘ sucker feet.’ And under the pia similar expansions unite with the fibres of this membrane. These swellings or sucker feet thus represent the union of the epiblastic and mesoblastic connective tissue. Under pathological conditions the astrocytes become enlarged and produce fibres in excess; they are said to multiply by direct division.

The cells of the *oligodendroglia* are distributed as satellites, especially in relation to medullated fibres, between which they form rows. They are supposed to play some part in the nutrition of the medullated sheath, but this has not been definitely established. They also occur as satellites in relation to nerve cells and to blood vessels. Although of small size, their cytological features correspond in various respects with those of the cells of the macroglia.

With regard to the *mesoglia* or *microglia*, one of the most interesting points is in connection with its development. The mesoglial cells do not appear in the central nervous system until the vessels are formed, and they are few in number till shortly before birth, when they invade the nervous tissue from the pia. This invasion occurs especially at spots where the pia is close to the white matter, and the crowds of invading cells are spoken of as 'fountains.' The cells travel in the white matter and afterwards become diffused through the grey matter. They also are often related to nerve cells and to blood vessels as satellites. As has been mentioned above, in their general behaviour in pathological conditions the mesoglial cells resemble the histiocytes of ordinary connective tissue.

DEGENERATIVE CHANGES

In some cases disturbance of nervous function is found to be due to structural alterations in the neurons, but in others no change to form an anatomical basis for the disturbance is discoverable. The alterations met with are mainly of a retrogressive or degenerative nature, and they may be primarily produced by the direct action of toxins, diminished blood supply, etc.; or, on the other hand, they may result in one part of the neuron from damage to another part, for example, the changes in the axon when the cell body is destroyed. The latter, which may be called 'secondary degenerations,' may be conveniently considered first.

Secondary Degenerations. The first of these is the well-known *Wallerian degeneration* which occurs in an axon when it is cut off from its neuron. This is readily intelligible on the neuron theory, according to which the axon is part of the nerve cell, and corresponds with the general law that a portion of a cell without a nucleus decays and dies. The changes in the axon, which are probably of autolytic nature, consist in irregular swelling and varicosity, followed by the formation of globules and granules and later by their absorption. The disturbance is reflected in the medullary sheath, the myelin becoming broken up into fatty globules stainable by Marchi's method. The degeneration of the myelin, which is readily detectable by the staining reaction, may be seen sometimes three or four days after the lesion; the primary and essential change, however, resides in the axons. After degeneration of myelin has occurred, the fatty globules are gradually absorbed, mainly by mesoglial phagocytes, but where large tracts are degenerated they persist for a considerable time; ultimately, however, they disappear.

The other form of secondary degeneration, which has been more recently recognised, is that which occurs in the neuron when its axon has been destroyed or injured—*retrograde degeneration*. The changes are sometimes spoken of as being reactive in nature, and the term *réaction à distance* has been applied by French writers. When a motor nerve, for example the hypoglossal, is cut across, changes begin to appear in the related neurons two or three days afterwards, and reach their maximum about two weeks later. The chromophile elements, or Nissl's granules, gradually lose their configuration and break down into small dust-like particles which are slowly absorbed. The process, which is called *chromatolysis*, appears first around the nucleus and then extends to the periphery. The whole cell becomes pale in appearance and at the same time somewhat swollen; its nucleus becomes eccentric in position, and may even form a slight bulging on the surface of the cell. These changes may be followed by a period of restitution which may not be completed till the end of three months, the appearance of the cell then returning to its normal condition. In some cases, however, this does not occur; on the contrary, the nucleus may break down or become extruded from the cell and the latter then disintegrates and disappears. Changes similar to those described are seen also in sensory neurons, and they take place rather more rapidly than in the case of motor neurons. To what extent these two results—repair or ultimate loss of the cell—occur, cannot be said to be fully determined. It seems, however, to be well established that destruction of the long fibres in the spinal cord is followed by gradual disappearance of the corresponding neurons. This has been found to be the case, for example, in the motor neurons in the cortex when the pyramidal fibres have been interrupted, and also in Clarke's column when the direct cerebellar tract has been the seat of the lesion. On the other hand, in the case of the lower neurons, restitution after the occurrence of chromatolysis appears to be the rule, and it is evident, of course, that if the neurons became destroyed the process of regeneration in the peripheral axons could not take place.

In addition to these secondary degenerations, another form has been described called *tertiary* or *trans-neuronal*. This means that a degenerative change passes, from a neuron to the arborisations of the adjacent neuron with which it is functionally connected, or in a reverse direction from the arborisations to the neuron. This atrophic change has been found, for example, in the cells of the nucleus cuneatus and nucleus gracilis when the posterior columns have degenerated; similarly it may happen in the motor neurons in the anterior cornua when the pyramidal fibres have been degenerated. It cannot yet be stated, however, under what conditions such changes occur and what is their significance.

Primary Degenerations. Under this term we include the structural changes produced *directly* by toxic action or impaired nutrition, the latter usually being the result of vascular disease. The various causes will be described below, but here reference may be made to their main features. Degenerative changes in the nerve cells result from the action of a great many poisons, but they are in no way specific, that is, peculiar to the particular poison. They may be of acute or of chronic nature. *Acute toxic action* is manifested chiefly by a swelling of the cell and diminution or disappearance of the Nissl's granules or chromophile substance, and by enlargement and pallor of nucleus, sometimes with eccentric position. Such changes correspond in a general way with those seen in secondary degeneration (p. 716), and are often indistinguishable from them. It is to be noted that actual *necrosis* of nerve cells with disappearance of nuclei and diffuse staining of the cell body, followed by disintegration, is met with chiefly in acute inflammations, such as epidemic encephalitis and poliomyelitis, or where the blood supply is cut off.

The effects of *chronic toxic action* are shown by shrinking of the cells, often with loss of finer structure and increase of chromophile substance, loss of normal outline and processes, vacuolation, etc., and these changes may be followed ultimately by death and disappearance of the cells. Accumulation of brownish pigment of lipoid nature, the so-called 'fuscous degeneration,' is sometimes a prominent feature in atrophy of the cells, especially in senile conditions; this change in itself, however, cannot be regarded as of much significance. A very important fact is that the actions of various poisons, the nature of most of which is unknown, may be evidenced by change first of all in the extremities of the axons; these degenerate and the degeneration gradually extends towards the neurons. It is manifest that in such chronic toxic conditions, degenerative changes met with in the nerve cells may be partly the direct result of the toxic action itself and partly secondary to the damage in their axons.

Lenticulate Degeneration. This affection, which was first described by Kinnier Wilson, is a rare condition, but one in which the changes are of very striking and suggestive character. It is met with chiefly in adolescence and early life, and although the total number of cases recorded is still small, it shows a clear tendency to run in families, as many as three cases having occurred in the same family; there is, however, no evidence that it is hereditary. Degenerative changes occur in the lenticulate nuclei, especially in the putamen, which, as the disease progresses, become somewhat softened and of worm-eaten appearance, whilst ultimately they may be excavated and changed into spaces containing fluid. Degeneration and disappearance of the nerve cells, attended by overgrowth of neuroglia, occur first; and then the proliferated neuroglia becomes softened and disappears, its place being taken by fluid. Wilson found no evidence that the lesions are due to arterial disease and obstruction, and the distribution and symmetry of the lesions also appear to be against such a possibility. Some degeneration may be present too in the caudate nuclei, but the pyramidal fibres are practically intact, as is likewise the spinal cord. The resulting symptoms are mainly muscular tremors and spastic condition of certain muscles, and Wilson considered that these are due to loss of the controlling influence of the nuclei on the motor fibres. It is of special interest to note that the condition is associated with a marked cirrhosis of the liver, and he regarded the lenticulate degeneration as probably the result of toxins derived from the liver. The etiology, however, is quite obscure. There is no evidence that either the cirrhosis or the brain lesion is due to syphilis or alcohol.

In connection with this disease it is of interest to note that in severe jaundice occurring in infants after birth, especially in icterus gravis neonatorum, there occurs a bile staining of certain parts of the brain which is known as Kernicterus. The parts chiefly affected are the basal ganglia, subthalamic nuclei, cornu Ammonis and fascia dentata. Further, in a small number of cases there has been found to follow in the affected parts overgrowth of neuroglia with loss of nerve cells, these structural changes being attended with serious nervous symptoms. Whether this condition is related to Kinnier Wilson's disease, however, has not yet been determined.

Atrophy. A general atrophy of the brain is met with in conditions such as senile dementia, chronic alcoholism and especially general paralysis of the insane ; in all of these cases there is wasting, especially of the grey matter, and there may also be a certain increase of consistence. A more limited degree of atrophy occurs, too, as part of the changes in old age. When the atrophy is distinct, the convolutions become more rounded and the sulci widened, so that there is an excess of fluid in the subarachnoid space. The pia-arachnoid, especially over the vertex, is often thickened and opalescent in appearance, and, owing to the excess of fluid in the meshwork of the arachnoid, the sulci appear to be filled with semi-gelatinous material. In a similar way the shrinking of the brain substance is attended by enlargement of the ventricles, so that they contain fluid in excess of the normal. The changes underlying atrophy of the brain vary in different cases. There may be a simple general wasting without any distinct histological change, although in senile cases there is often an accumulation of brownish yellow pigment in the nerve cells—the so-called fuscous degeneration. In other cases where there is extensive disease of the arterial twigs, atrophy and disappearance of nerve cells occur, and this is often attended by an increase of the neuroglia ; not infrequently there are also microscopic areas of softening and these likewise lead to glial overgrowth. Such changes are a prominent feature in senile insanity. In general paralysis of the insane two processes are found to be present side by side, namely, overgrowth of neuroglia on the one hand and a progressive degeneration and disappearance of nerve cells on the other, the whole condition corresponding to a diffuse chronic encephalitis (p. 758).

EFFECTS OF INJURIES

All degrees of injury to the brain may be met with. In extreme cases the calvarium may be broken in and a considerable part of the brain pulpified. Bruising of the brain is met with at two chief sites, viz. at the site of injury and at the opposite pole of the brain ; the latter injury is said to occur by *contre coup*. It is, however, quite common to find no visible lesion where the blow was struck and considerable laceration at the opposite pole. In fact this is the rule unless the blow has been very severe or accompanied by fracture at the site of impact. The *contre coup* injury apparently results from a wave of compression or disturbance from the site of injury being suddenly arrested by the hard base of the skull. As the blow is often on the occiput, the under surface of the frontal and temporo-sphenoidal lobes usually shows superficial laceration, the disintegrated brain substance being mixed with blood (Fig. 448). This will be on one side or both sides, in accordance with the site of the blow. Along with the superficial laceration mentioned, there is often a considerable amount of diffuse subarachnoid hæmorrhage, especially along the sulci. There may be also escape of blood from the lacerated brain tissue into the subdural space, where it may form a thin layer. Œdema of brain, too, is an important occurrence; it is most marked in the neighbourhood of lacerations, but it may be more general. In conjunction with actual hæmorrhage it plays an important part in increasing intracranial pressure and leading to symptoms of compression. Such cerebral lesions may be associated with fracture of varying degree, which is usually at the base, but laceration of the surface of the brain may occur without fracture. It is of importance to note that whilst laceration and hæmorrhage are usually superficial, hæmorrhages are occasionally met with around the ventricular system, e.g. in the inner aspect of the optic thalami or around the aqueduct of Sylvius. When the cranial cavity is compressed at the time of injury, there is a momentary forcing of a certain amount of fluid downwards into the spinal canal, and it is possible that the disturbance of fluid in the ventricles may lead to such hæmorrhages. They are undoubtedly secondary to injury and are not to be interpreted as being of spontaneous nature and thus possibly the cause of the fall and injury. In the case of a person falling on the feet, fracture at the base may be produced, and it is accompanied by laceration of the under aspect of the brain. When there is escape of blood into the subdural space, and the patient survives for some time, the blood becomes brownish in colour, and is organised from the dura so that a membranous

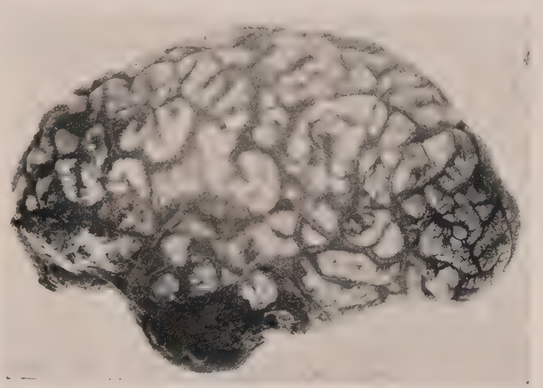

Fig. 448.—Laceration by *contre coup* of the under surface of frontal and temporo-sphenoidal lobes; also diffuse subarachnoid hæmorrhage.

formation results (see 'pachymeningitis hæmorrhagica' p. 721). The lacerated brain substance assumes a brownish-yellow colour. In cases of head injury the cerebro-spinal fluid obtained by lumbar puncture often contains red corpuscles in varying amount. At a later period the fluid assumes a brownish or yellowish colour owing to changes in the hæmoglobin.

A specially important occurrence is laceration of the middle meningeal artery or of its branches, which is not uncommon in cases of fracture of the squamous part of the temporal bone. The blood accumulates outside the dura and gradually separates it from the bone, so that ultimately a large saucer-shaped clot forms which produces compression of the brain (Fig. 449). In such cases symptoms may be little marked immediately after varying degrees of initial concussion and the patient may regain consciousness; but they gradually appear later, and ultimately coma develops. Diagnosis of the condition is of high importance, as it is amenable to surgical treatment. Fracture of a bone may sometimes lead to laceration of a venous sinus with extensive bleeding into the subdural space.

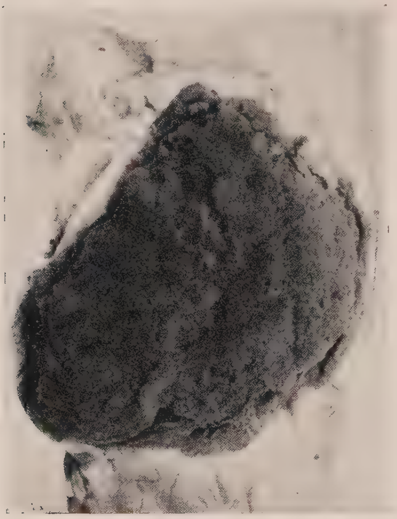

FIG. 449.—Large saucer-shaped extra-dural Clot from a case of rupture of middle meningeal artery. × $\frac{3}{4}$.

In the great majority of cases of death following head injury some of the above described changes are usually distinct. Occasionally, however, there may be only slight subarachnoid hæmorrhage, scattered petechiæ in the brain substance or some general œdema. It is important to note that in cases of fracture of the base death may result some days later from septic meningitis, the result of bacterial infection from the nasopharynx or a sinus.

FUNCTIONAL EFFECTS. The symptomatology of head injuries is a complex subject, but two main factors are concerned, viz. *concussion* and *compression*. A sufficiently severe blow is followed by *concussion*, there being sudden loss of consciousness, general flaccidity of muscles, etc. This may be soon recovered from as in the 'knock-out' blow of prize fighters, or it may be prolonged and followed by the symptoms of shock which in severe cases may be complicated by the symptoms of compression. The mechanism of concussion is still a matter of dispute. It has been attributed to sudden intense anæmia brought about by compression of the cranial cavity, by sudden pressure of the cerebro-spinal fluid on the medulla, and again to molecular disturbance of the nerve cells, this last probably being the most important. When a patient regains consciousness after concussion there sometimes follows a period of cerebral irritation which has been ascribed to œdema of the brain substance.

When death follows within a day or two after severe injury, it is mainly due to *cerebral compression* brought about partly by effused blood and partly by œdema of the injured brain substance. The combined effect of these two leads to coma, and also to interference with the cerebral circulation and thus to deficient supply of blood to important centres. Those in the medulla suffer from anæmia, and it is believed that the full and bounding pulse met with in compression represents a compensatory mechanism for improving the circulation. Ultimately this may be insufficient and death follows. The onset of compression is very well illustrated in the case of extradural hæmorrhage just described. When the patient recovers from the earlier effects of the injury, processes of healing occurs in the lacerated areas resulting in gliosis and this may give rise to symptoms often of an epileptic type, at a later period. This is readily understood in the case of the grosser lesions, but it is important to realise that there are also in head injuries multiple minor effects on the brain substance, discoverable only on microscopic examination, and that the healing of these may lead to later functional disturbance. It is, however, remarkable that in cases of fracture of the skull with evidences of severe brain injury there may be complete return to normal function after a time.

Injuries of the *spinal cord*, like those of the brain, are of all degrees of severity. In cases of fracture, dislocation, bullet wounds, etc., the cord may be directly lacerated, or even torn across. Apart from such extreme cases, the cord may be damaged from severe concussion, blows on the back, falls on the feet, etc., and hæmorrhage may occur either outside or inside the dura. Lesions are met with in the substance of the cord itself, and these are of the nature of softenings of all degrees or of hæmorrhages, and the two lesions may be combined. Hæmorrhage occurs especially in the grey matter posteriorly, and tends to extend upwards and downwards through several segments. In cases of hæmorrhage into the cord, or hæmatomyelia, the blood undergoes the usual changes, and ultimately an elongated cavity with capsule may result, which may simulate syringomyelia (p. 783) in character. Apart from these grosser effects it is not uncommon to find partial degeneration of fibres in the cord, which may extend through several segments. This is apparently the result of sudden bending or stretching of the cord at the time of injury. Functional disturbance may be produced in this way.

The term *pachymeningitis hæmorrhagica* has been applied to a condition in which membranous layers of brownish colour are found on the inner aspect of the dura. The term is incorrect as the condition is not of inflammatory nature, but simply the result of hæmorrhage into the sub-dural space. Such membranes, which are commonest over the cerebral hemispheres, vary in thickness, sometimes being a mere film, sometimes forming a thicker layer with brownish fluid in the central parts. They are met with in conditions of insanity, especially general paralysis in which they are not uncommon, also in senile insanity and in chronic alcoholism. It may be mentioned that similar membranes may be found in cases of fracture of the skull with escape of blood into the sub-dural space, when the patient has died some weeks after the injury. If blood enters the sub-dural space from any cause, it becomes diffused underneath the dura and later coagulates. A reaction is set up whereby it becomes organised from the side of the dura ; young blood vessels and connective tissue cells penetrate the layer of clot and gradually organise it, whilst the red blood corpuscles become disintegrated and form various kinds of pigment ; a layer of endothelium also grows over its surface from the lining of the dura. In this way a brownish membrane of varying thickness is formed. Hæmorrhages may occur again into its substance and the membrane may come to have a somewhat laminated appearance. The membrane is usually non-adherent to the surface of the arachnoid, but sometimes adhesions form.

CIRCULATORY DISTURBANCES

Of these, by far the most important result from arterial closure, on the one hand, and hæmorrhage on the other. We may, however, refer first to some less important conditions. The amount of blood present in the brain *post mortem* varies greatly, and in judging of this the cranial cavity ought to be opened first, as, when the thorax is opened and the heart removed, a considerable amount of blood drains off through the veins. *General anæmia* is seen in such conditions as severe hæmorrhage, heart failure especially in aortic disease, and it is sometimes a marked feature in association with œdema in cases of nephritis. The brain appears very pale in pernicious and other anæmias owing to the condition of the blood. *Local anæmia* is usually produced by interference with the blood supply in arterial disease, and the obstruction may be complete or incomplete. It results also when any gross lesion presses on the brain substance and interferes with circulation through it. The effects are described below, in connection with arterial obstruction.

Chronic venous congestion of course occurs in the usual conditions, such as chronic cardiac and pulmonary disease. Recent venous engorgement is merely an agony condition and depends on the state of the circulation at the time of death. It is usually a very marked feature in cases of opium poisoning, where the veins are greatly distended, and the whole brain substance, especially the grey matter, is intensely congested and of purplish colour. The small veins in the white matter are likewise engorged, and when a section is made, small drops of blood escape from them, forming the so-called *puncta cruenta*. With regard to *acute congestion*, a distinction is to be made between that of the membranes and that of the brain substance. The former may represent the earliest stage of an infective process and organisms may be present. For example, this may be the case in lobar pneumonia, and pneumococci may sometimes be found on microscopic examination, though no actual exudate is present. Acute congestion of the brain substance, most noticeable in the grey matter, may be met with in fevers and other infective conditions, and it is said to be a prominent feature in cases of sunstroke. It is observed locally in the region of inflammatory changes, e.g. in encephalitis lethargica (p. 741). The significance of acute congestion must be judged of in connection with the other conditions present.

A general œdema of the brain is seen especially in cases of nephritis, especially where there is general renal œdema, and it is accompanied by anæmia. The accumulation of fluid occurs especially in the white matter of the brain, and when the brain is cut with a dry knife the surface becomes wetter afterwards, owing to the gradual escape of the fluid from the tissue on to the surface. The condition is sometimes associated with uræmia, although it is not to be regarded as the cause of the latter. Either may occur without the other. It apparently plays a part, however, in producing hypertensive convulsions by increasing ischæmia of the brain substance, especially in nephritis in the earlier years of life. In some cases the œdema may be so great as to cause a distinct cerebellar cone (*vide infra*). Œdema of the brain may also occur from head injuries (p. 719). *Local œdema* is often seen in the neighbourhood of gross lesions, such as tumour growths, abscesses, hæmorrhages, etc., and is the result of interference with the blood supply by pressure. When it has lasted for some time the nerve fibres suffer, their myelin becoming broken up into globules and a certain amount of demyelination resulting. (Greenfield.) The brain substance is paler, moister and of rather diminished consistence, and, when the circulatory disturbance is more marked, it merges into the condition of anæmic softening. A true *inflammatory œdema* may occur by diffusion of toxins from some inflammatory focus, e.g. a cerebral abscess.

A condition often met with and of some importance in the examination of the brain is *flattening of convolutions*. It presents a contrast in nature to œdema of the brain and its membranes. Any gross lesion in the ventricles or in the brain substance tending to add to the cranial contents can do so only by displacing the cerebro-spinal fluid. The convolutions are pushed out and flattened against the bone, and thus the sulci become narrowed and fissure-like; at the same time the brain substance appears drier as the fluid is pressed out of the perivascular spaces. Flattening of the convolutions is thus seen in such conditions as hydrocephalus, cerebral hæmorrhage, tumour growth, etc. A condition often associated with flattening of the convolutions is the formation of what is known as a 'cerebellar cone.' It is due to the medulla and adjacent tissue of the cerebellum being pushed downwards into the foramen magnum, a cone-like structure being formed by moulding from pressure. When fully formed it will interfere with the passage of the cerebro-spinal fluid downwards to the spinal canal and tend to increase the intracranial pressure. It is important to note that when there is a tendency to this condition the sudden withdrawal of cerebro-spinal fluid may aggravate it.

Cerebral Hæmorrhage

Hæmorrhage into the brain or its membranes may occur in the form of multiple minute foci, and is then of importance chiefly as a manifestation of the disease which causes it. Or, on the other hand, it may be of considerable size, usually the result of the sudden bursting of an artery, and may give rise to serious and often fatal results, generally indicated by the term ‘ apoplexy ’; though closely similar symptoms may be produced by cerebral softening.

Cerebral hæmorrhage in the ordinary sense, which leads to serious effects, may be said to be of two main types. In the first, which is the commoner, the hæmorrhage occurs from, and is the result of disease of, the *nutrient vessels* which penetrate deeply. In the second it is due to the bursting of an aneurysm of the *circle of Willis or its branches*. We shall consider these two types separately.

(*a*) Hæmorrhage from a nutrient artery is the common form in the later years of life, giving rise to apoplexy. It is most frequently the result of arteriosclerosis attended with high blood pressure, hypertrophy of the left ventricle, fibrosis of the kidneys, etc., and in these circumstances it is not uncommon, even under the age of fifty. Hæmorrhage occurring without high blood pressure is met with mainly in old age, and is the result of extensive atheroma or hyaline degeneration in the minute arteries. Cerebral hæmorrhage is often described as being due to the bursting of a miliary aneurysm (p. 315), but, whilst this may sometimes be the case, our experience is that in most instances no aneurysms can be found. It is further to be noted that many of the small swellings to be found on the arteries in the region of a hæmorrhage are due simply to small extravasations of blood in the walls of the arteries or in their perivascular spaces—dissecting or false aneurysms.

By far the commonest site of this type of cerebral hæmorrhage is the region of the basal ganglia ; the pons comes next in order of frequency, whilst hæmorrhage into the superficial parts of the brain, into the crura, medulla, and cerebellum, is relatively rare. The so-called ventricular hæmorrhage is usually due, as can be found on careful examination, to rupture from an adjacent hæmorrhage in the substance, most frequently in the head of the caudate nucleus or in the thalamus. Hæmorrhage in the basal ganglia usually occurs from the lenticulo-striate arteries, which are branches of the middle cerebral and thus on the direct line of blood flow from the carotid ; they enter at the anterior perforated spot, pass upwards in the external capsule and then curve inward through the lenticulate nucleus and internal capsule. Charcot applied the term 'artery of cerebral hæmorrhage' to the lenticulo-striate artery, though there are several arteries to which the latter term is applicable. Hæmorrhage is not uncommon from the lenticulo-optic and other branches in the optic thalamus and adjacent parts.

When hæmorrhage occurs, the effused blood forms a large blood clot, often oval in form and may measure two or three inches in long axis (Fig. 450). It tears up and destroys the structures around, and at the margin there are often secondary small hæmorrhages, the result of laceration. When a hæmorrhage bursts into the lateral ventricles they become distended with blood, the ventricle on the same side as the hæmorrhage usually to a greater extent, and the blood passes down the aqueduct of Sylvius and through the foramina in the roof of the fourth ventricle. Sometimes some laceration with secondary hæmorrhage may be present around the aqueduct. The blood then reaches the subarachnoid space and may there spread widely over the structures at the base of the brain; it may also pass downwards over the spinal cord. Occasionally, though not often, a hæmorrhage in the substance may break through directly to the surface of the brain. At a post-mortem examination in a case of large cerebral hæmorrhage, the convolutions are seen to be flattened and dry in appearance from the pressure, and this is often more marked over the affected hemisphere, which may bulge somewhat. Hæmorrhage into the pons may be of considerable

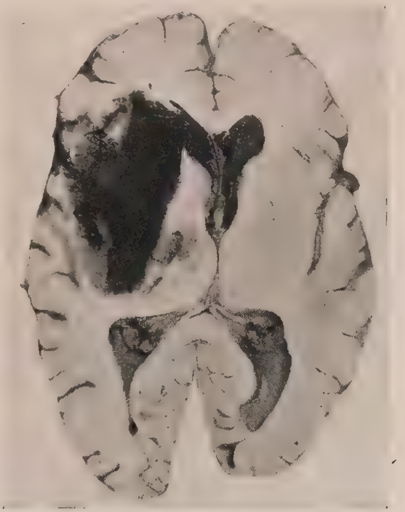

Fig. 450.—Large recent Hæmorrhage on the left side which has ruptured into the lateral Ventricles.

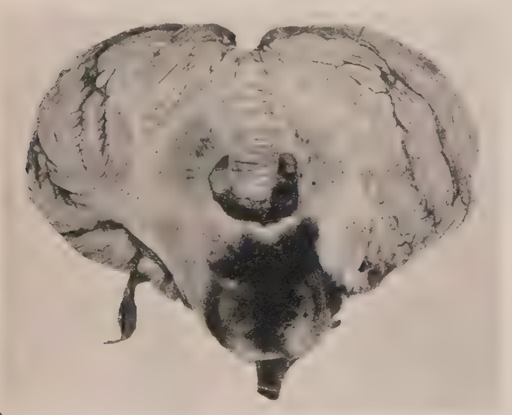

Fig. 451.—Hæmorrhage into Pons Varolii.

size and cause distinct enlargement; the effused blood is often broken up by the transverse fibres. Occasionally rupture into the fourth ventricle follows (Fig. 451).

In a case of cerebral hæmorrhage, it is not uncommon to find in the unaffected basal ganglia evidence of previous hæmorrhages in the form of small spaces containing brownish fluid. Small softenings also may be met with as the result of the arterial disease (p. 730).

(*b*) When the hæmorrhage is from the circle of Willis or one of its branches, a ruptured aneurysm can usually be found, though not always. The characters and conditions of occurrence of aneurysms in this situation have already been discussed; it is sufficient to recall that these may be met with at an early period of life and quite apart from any general arterial disease, and are now generally known as congenital aneurysms. The aneurysm may be in any position; for example, on the basilar, on the anterior communicating, on a branch of the anterior cerebral overlying the corpus callosum, etc. In the rare cases where the cause of the aneurysm has been infective embolism, the commonest site has been, in our experience, in connection with one of the middle cerebral arteries (p. 728). Occasionally an aneurysm may be due to atheroma. In nearly all cases of rupture of an aneurysm of the circle of Willis or a branch there is subarachnoid hæmorrhage, which is often diffuse and extensive; the aneurysm is then to be looked for where the hæmorrhage is thickest. There is often also hæmorrhage into the adjacent part of the brain; and sometimes this is extensive and passes directly inwards as if, on sudden rupture of the sac, the blood were shot violently into the brain substance.

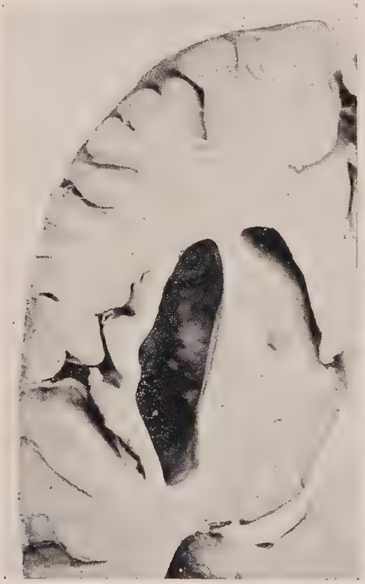

FIG. 452.—Old Apoplectic Cyst on left side of Brain.

The cyst involves chiefly the external capsule and the outer part of the lentiform nucleus.

In any case of recent cerebral hæmorrhage, the blood forms an ordinary dark-coloured clot and retains this appearance for several days. At the end of about a week it comes to have a brownish colour at the periphery, and this change in colour extends and becomes more marked as time goes on. The clot becomes softened at the margin and is thus surrounded with a brown fluid, while neuroglial proliferation leads to the formation of a capsule. Ultimately the clot, as such, disappears and fluid remains, which gradually becomes paler in colour. The ultimate result is the so-called apoplectic cyst, which has a pigmented wall owing to the presence of hæmatoidin and hæmosiderin in the tissue; the contents may ultimately have merely a yellow colour (Fig. 452). If the hæmorrhage be relatively small, it may be entirely replaced by proliferated neuroglia, which contracts and forms a cicatrix, usually of orange or brown colour.

It may be added that hæmorrhage on the surface of the brain in the form of multiple irregular patches may be produced by obstruction of the superior longitudinal sinus, as will presently be described.

The *effects of cerebral hæmorrhage* may be said to be both focal and general in character. The former effects are produced by the actual destruction of cells and fibres, and are of the nature of paralysis and permanent loss of function. Pressure of the effused blood on the surrounding tissue, however, may cause symptoms either of paralysis or of irritation; and these may be recovered from when the pressure diminishes. A large hæmorrhage in the interior of the brain will cause in addition a general compression of the brain substance outwards, as is shown by the flattening of the convolutions, and will thus lead to coma, which is usually followed by a fatal result.

Multiple small hæmorrhages are met with chiefly in certain blood diseases and in severe infective conditions; examples of the first are pernicious anæmia, purpura, scurvy, leukæmia, and of the second septicæmia, typhus, smallpox, etc. They are usually in the form of petechiæ, though sometimes they are larger, and occur especially in the soft membranes. In leukæmia, hæmorrhages of considerable size, single or multiple, occasionally occur in the brain substance and are apparently the result of the formation of leucocyte thrombi in the vessels. In most cases of infections the hæmorrhages are the result of toxic action on the capillary walls, but sometimes organisms are present. In some cases of very acute staphylococcus infection, for example, capillaries plugged with cocci may be found in the hæmorrhagic spots in the brain substance. Hæmorrhage may also be a concomitant of meningitis, and diffuse hæmorrhage in the subarachnoid space is a prominent feature of meningitis caused by the anthrax bacillus.

Arterial Obstruction—Cerebral Softening

The effect of closure of an artery in the brain is cerebral softening in the part which the collateral circulation is unable to supply with sufficient blood to keep it alive (p. 25). Important results follow also when the blood supply is *diminished* by narrowing of the lumen of small arterial twigs, but to a degree insufficient to cause visible softening. In this case there may occur degeneration or necrosis of the nervous tissue, while the neuroglia retains its vitality. The degenerated remains of nerve cells and fibres become absorbed, and there is overgrowth of the neuroglia, so that a patch of *sclerosis* results. This process is quite analogous to the starvation atrophy with fibrosis which occurs as the result of arterial narrowing in the heart muscle, kidneys, and other organs. Areas of sclerosis produced in this way are a prominent feature in senile dementia, and they are common also in general arterial disease, especially in old people.

Complete obstruction of arteries in the brain is usually produced by embolism or by thrombosis occurring locally ; it may result also from obliteration of arterial twigs from syphilitic or tuberculous endarteritis. The resulting cerebral softening is often described as being of white, red, or yellow variety. As a rule, a recent softening is of the pale or anæmic type, but in some instances it is red, this latter appearance being due to numerous minute hæmorrhages into the softened tissue (Fig. 453). The area has then usually a dappled appearance, and can thus be distinguished from the uniform clot of ordinary cerebral hæmorrhage. It is difficult to explain why softening should be sometimes of this red variety, but it is possible that in some cases marked venous congestion may aid its occurrence. Old softenings may have a yellowish colour due to alteration in any blood which may be present.

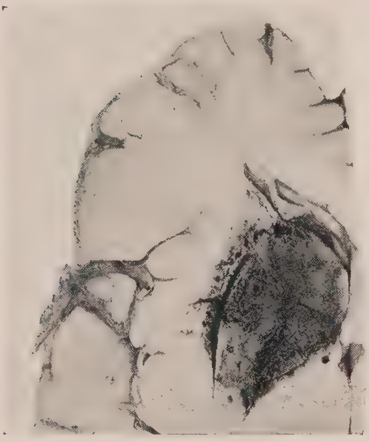

FIG. 453.—Red Softening of head of left Caudate Nucleus and of the parts behind.

Note the scattered hæmorrhages in the softened area.

The commonest site of embolism is a middle cerebral artery, and the left is more frequently plugged than the right ; it is generally supposed that this is because the left carotid is more directly in the line of the blood stream in the aorta. Embolism of other cerebral arteries also occurs, but is much less frequent than that of the middle cerebrals. The embolus usually comes from vegetations on the mitral or aortic cusps, sometimes from a thrombus in the left auricle or ventricle or in the aortic arch, and occasionally as material separated by ulceration from an atheromatous patch. When a middle cerebral is completely blocked, softening does not occur in the whole anatomical area supplied by the vessel, as certain parts are sufficiently nourished by the collateral circulation. The internal parts suffer most, and there is usually softening to a varying degree in the internal capsule, lentiform nucleus, external capsule, claustrum, and anterior part of optic thalamus (Fig. 454). The superficial softening, which varies greatly in extent, is most marked around the island of Reil and the fissure of Rolando, but in cases where the collateral circulation is interfered with by arterial disease, or by weak heart action, the softening of the cortex may be more extensive. When the obstruction does not involve all the branches of the middle cerebral, the softening will vary accordingly.

It may be added that, whilst under normal conditions cutting off of the blood supply through one internal carotid leads to no serious disturbance owing to the collateral anastamosis through the circle of Willis, extensive softening may result when there is marked arterial disease or where the circulation is imperfect. Under these conditions thrombosis or embolism of the internal carotid may lead to a varying amount of softening, especially in the region of distribution of the middle cerebral artery; and, of course, a similar result may follow when either that vessel or the common carotid is ligatured.

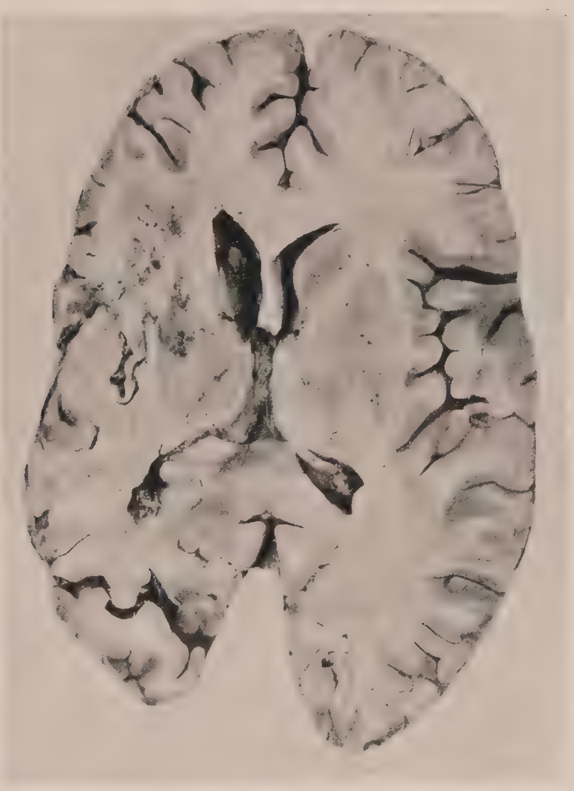

Fig. 454.—Comparatively recent Softening on the left side of the Brain, showing the disintegration of its substance in the Basal Ganglia and around the Island of Reil.

Structural Changes. When the brain is examined a short time after the plugging has occurred, little change may be visible. The surface of the affected part is often rather more congested than that of the rest of the brain owing to collateral hyperæmia, but this soon passes off. Occasionally the part is a little swollen, owing to slight œdema. Soon, however, softening occurs and this at the earliest stage is best demonstrated by running a stream of water over the cut surface, when the affected tissue shows a tendency to disintegrate. In two or three days the part has become distinctly softened; it is pulpy, the anatomical markings are lost, and it gradually comes to resemble a thick whitish emulsion. When this is examined microscopically, it is found to contain a great many granules and fatty globules, degenerated remains of cells and fibres, whilst a prominent feature is the presence of 'compound granular corpuscles' with fatty globules in their interior (Fig. 455). These are mesoglial cells which become enlarged and act as phagocytes. At a later period the fluid gradually becomes less turbid, whilst the neuroglia at the margin of the area proliferates and forms a capsule. The final result may be a space or 'cyst' containing clear fluid, limited by a fairly definite wall and sometimes broken up by septa (Fig. 456). In the case of an old cortical softening the soft membranes are somewhat thickened and opaque, and underneath there is usually an adherent layer of brownish-yellow brain tissue, degenerated but not completely softened. Below this, again, strands of thickened neuroglia may extend into a collection of fluid.

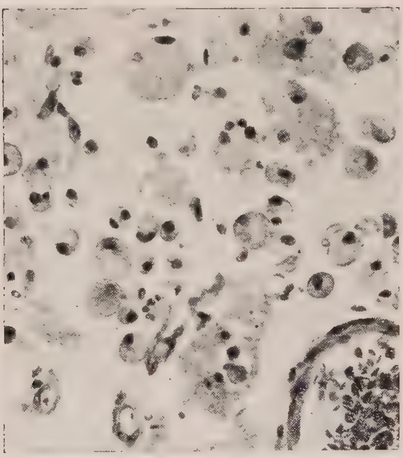

Fig. 455.—Margin of cerebral softening showing characters of 'compound granular corpuscles'—enlarged mesoglia cells. (A. C. L.) × 250.

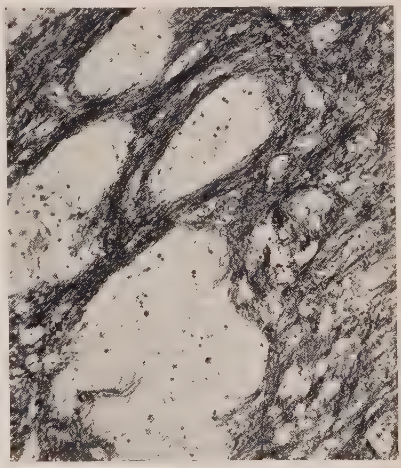

Fig. 456.—Portion of cerebral softening at later stage, stained to show thickened neuroglia with spaces containing fluid between. (A. C. L.) × 80.

An important result of softening, of course, is the Wallerian degeneration in the nerve fibres which have been interrupted in their course, or of which the corresponding neurons have been destroyed by the lesion. And when motor fibres have been interrupted, say in the internal capsule, there occurs a secondary degeneration in their corresponding neurons, the large pyramidal or Betz cells of the cortex (p. 716). It is mainly to old softening, involving the internal capsule, that long-standing hemiplegia is due, since in cases where a hæmorrhage has been of sufficient size to produce the interruption, death usually occurs within a relatively short time. The descending degeneration in the motor tracts is followed by absorption of the myelin and overgrowth of the neuroglia, and can then be readily followed by the Weigert-Pal method. The degeneration of the pyramidal fibres is seen in the middle of the anterior part of the crus ; in the pons the degenerated fibres are broken up into bundles by the transverse fibres, while in the medulla the anterior pyramid is degenerated. When later there is shrinking of the sclerosed parts, distinct asymmetry may result ; this is especially noticeable in the medulla, where the affected pyramid is shrunken and grey in appearance. In the cord, both the crossed pyramidal tract on the other side and the direct pyramidal are affected to their lower terminations in the anterior cornua.

Softening resulting from *thrombosis* may affect practically any part of the brain ; but the middle and posterior cerebrals, basilar, or their branches, are common sites of obstruction from this cause. When the basilar is thrombosed, softening occurs chiefly in the pons, and one half may be more affected than the other ; as a result, as shown by Marchi's method, the pyramidal tracts of the two sides are unequally involved. In syphilitic disease, even at an early stage, a certain amount of softening is common in the superficial parts of the brain and cord, as the result of arterial changes in the meninges (p. 766). In cases of arteriosclerosis, it is not uncommon to find in the basal ganglia multiple minute spaces resulting from softening (small hæmorrhages also in this region may produce small cavities, but in this case the contained fluid has a brownish tint from the altered blood). Areas of softening from arterial thrombosis occur also in the cortex, and vary greatly in extent and shape.

We may mention that in a case of Raynaud's disease observed by us, where there was gangrene of portions of the extremities and tip of the nose, several softened areas of considerable size were present in the surface of both hemispheres. There was no evidence of disease of the arteries, thrombosis, or embolism, and the softening had apparently resulted from spasm of the arteries.

Venous Obstruction. The most important form of this occurs as a result of thrombosis in one of the sinuses, and two forms of thrombosis are usually distinguished, the *marantic* and the *infective :* the latter is often attended by suppuration within the sinus. *Marantic thrombosis* is most frequent in poorly nourished children during the course of acute infections, e.g. gastro-enteritis ; but it is sometimes met with in adults in conditions of cachexia, or as a complication of infective fevers with exhaustion, or in chlorosis. In the production of thrombosis, impaired nourishment of the intima and sluggish circulation no doubt play a part, but it is possible that in some cases the process is started by organisms of mild virulence. The commonest site is the superior longitudinal sinus, and, when obstruction is complete, intense engorgement of the superficial veins occurs, often followed by irregular hæmorrhages on the surface of the brain. In a case of thrombosis of the straight sinus which we examined, similar hæmorrhagic areas were present in the walls of the third ventricle. *Infective thrombosis* is the result of direct spread of organisms from an inflammatory or suppurative condition in the neighbourhood. This is of common occurrence in the sigmoid sinus in cases of middle ear disease, although other sinuses may be affected in septic inflammations of bones. Acute meningitis or cerebral abscess may often follow, as is described more fully below.

Hydrocephalus

The term hydrocephalus is generally used as meaning *hydrocephalus internus*, a condition in which the ventricles are distended with fluid. *Hydrocephalus externus* is an accumulation of fluid under the arachnoid, where there is a local atrophy of the brain or other abnormality. This term is now little used. Distension of the ventricles occurs in two distinct forms, viz. *acquired hydrocephalus*, where the accumulation is due to recognisable gross lesions, and *congenital hydrocephalus*, the pathology of which is often obscure. Before considering the pathology of these conditions it will be convenient to consider some points with regard to the cerebro-spinal fluid.[1]

Source and Circulation of Cerebro-spinal Fluid. The source of cerebro-spinal fluid is now known to be the choroid plexuses of the ventricles. This has been recently demonstrated in a striking manner by the experiments of Dandy, who produced obstruction to the foramen of Monro on one side in the dog and found that dilatation of the corresponding lateral ventricle occurred ; on the other hand, when in addition to the production of obstruction the choroid plexus was removed, the ventricle became collapsed and smaller than that on the other side. It is thus shown that the fluid is formed by the plexuses and not by the ependyma lining the ventricles. Cerebro-spinal fluid is constantly being formed and it has been calculated that in the normal state it is renewed several times a day. When, however, there is a free outlet to its escape the amount formed may be enormous. The mechanism of production, whether by secretion or filtration, is still a disputed question, but the all-important fact is that when there is an obstruction to outflow the formation of fluid is not arrested but continues and leads to distension of the ventricles. The fluid formed in the lateral ventricles passes by the foramen of Monro to the third ventricle and then by the aqueduct of Sylvius to the fourth ventricle, being added to by the choroid plexuses on its way. From the fourth ventricle it passes through the foramina of Magendie and Luschka and thus reaches the subarachnoid space of the cisterna magna; it then passes to the cisterns at the base of the brain and thence spreads through the meshwork of the arachnoid all over the surface of the brain and spinal cord. The path of absorption is still a matter of dispute. According to one view it is by means of the Pacchionian bodies and smaller arachnoid villi which project into the venous sinuses, whilst another view is that the absorption takes place by the capillaries of the pia-arachnoid. It is clear, however, that by whatever channel the absorption occurs, the site of a large proportion of the absorption is the surface of the hemispheres, the amount absorbed from the spinal arachnoid being comparatively small.

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[1] For a detailed account see *The Cerebro-spinal Fluid in Clinical Diagnosis*, by J G. Greenfield and E. A. Carmichael ; London, 1925.

There is thus a constant circulation of cerebro-spinal fluid from the ventricles to the surface of the hemispheres, and serious obstruction at any point along the path of flow will give rise to hydrocephalus. It has long been recognised that common sites of obstruction are (*a*) the aqueduct of Sylvius and (*b*) the communications in the roof of the fourth ventricle between the latter and the subarachnoid space. There is, however, another site of obstruction, viz. (*c*) the base of the brain. It has recently been shown by Dandy that obstruction may result from inflammatory change involving the cisterns at the base of the brain. He demonstrated this by placing a strip of gauze soaked in iodine round the brain stalk just above the tentorium; the resulting inflammation produced thickening and a considerable amount of obliteration of the subarachnoid space, and thus hydrocephalus followed. He accordingly gave the name *non-communicating* hydrocephalus to the type where the fluid is prevented by obstruction (as in (*a*) and (*b*)) from passing from the lateral ventricles to the subarachnoid space, and *communicating* hydrocephalus to the type (*c*) where there is no such obstruction, the interference with flow being at the base of the brain. The two types of hydrocephalus may be distinguished by methods which can be applied during life. If an inert coloured fluid such as indigo carmine is injected into the lateral ventricles in the communicating type of hydrocephalus, it can soon be found in the fluid obtained by lumbar puncture; whereas, of course, it does not appear in the non-communicating type. The site of the obstruction in cases of hydrocephalus has been investigated also by cerebral pneumography. In this method a considerable quantity of cerebro-spinal fluid (60–80 c.c.) is removed by lumbar puncture, and air is injected to take its place. The air extends wherever there is free communication, this, of course, being aided by the position of the body, and can be seen as dark areas in an X-ray negative. In the communicating type of hydrocephalus the air passes into the ventricles but is arrested at the base of the brain, at the cisterns or beyond them, and does not spread over the hemispheres. In the non-communicating form the air is arrested at the roof of the fourth ventricle or at the aqeduct, according to the site of the obstruction ; on the other hand it passes to the surface of the hemispheres and can be seen in the form of small bubbles along the sulci. The absence of air in the sulci thus indicates that the obstruction is in the subarachnoid space at the base of the brain.

Acquired Hydrocephalus usually occurs as a result of *mechanical interference* with the flow of cerebro-spinal fluid from the ventricular system to the surface of the brain. It may also be due to inflammatory conditions involving the choroid plexuses and ventricular lining, e.g. in tuberculosis and cerebro-spinal fever (q.v.). In such conditions, however, mechanical factors are not infrequently involved.

Mechanical obstruction is of three chief kinds. (*a*) In the first place, it may be due to direct pressure on the aqueduct of Sylvius or on the fourth ventricle by a tumour or tuberculous mass. In fact it is one of the most important effects of any growth below the tentorium. Pressure may be exerted also on the veins of Galen or straight sinus, and the resulting venous congestion may lead to hydrocephalus or accentuate it. (*b*) The second mode of obstruction occurs as a result of chronic meningitis, which often leads to thickening and adhesions of the arachnoid round the fourth ventricle and obliteration of the foramina in its roof. In this way the normal path of flow to the subarachnoid space is interfered with. Such an occurrence is common in chronic tuberculous meningitis, posterior basal meningitis, and sometimes as a late result of acute meningitis, e.g. in cerebro-spinal fever. (*c*) In the third place the obstruction may be the result of inflammatory change involving the cisterns of the arachnoid at the base of the brain, the onward passage of the fluid to the surface of the hemispheres being thus blocked or interfered with, as already explained. This occurs in the inflammatory conditions just mentioned and appears to be a fairly common cause, as there is often no evidence of lesion in the roof of the fourth ventricle to explain the hydrocephalus. In all cases of acquired hydrocephalus the convolutions are markedly flattened and dry in appearance, and the sulci are narrowed. The functional effect is the production of symptoms of cerebral compression in varying degree. Another result often met with is that the medulla and the adjacent parts of the cerebellum are thrust downwards into the foramen magnum, producing a ‘ cerebellar cone ’ (p. 723).

Congenital Hydrocephalus. This condition may be marked at the time of birth, and sometimes to such a degree as to interfere with parturition. In other cases it is slight at birth and afterwards increases. The head may be enormously enlarged, the increase being chiefly in the antero-posterior and lateral directions ; it becomes more quadrangular in form, the vertex being somewhat flattened. The frontal region projects over the orbits, and the upper walls of the latter are drawn up more towards a vertical plane. The sutures are greatly widened, and the fontanelles much enlarged ; and ossification of them is delayed for a long time. There is a corresponding enlargement of the brain, and the convolutions are broadened out and flattened, while the sulci become shallow. The accumulation in the ventricles of fluid, which is clear and colourless, is often in remarkable amount and the lateral ventricles may be distended to such an extent that only about half an inch of brain substance may at places separate them from the surface (Fig. 457). The third ventricle also is dilated as a rule, but relatively to a less degree. It is remarkable how the brain substance adapts itself to the altered configuration and relations; and, while in most cases there is interference with the mental functions and idiocy may be present, in some instances the child may be wonderfully intelligent even when the hydrocephalus is marked.

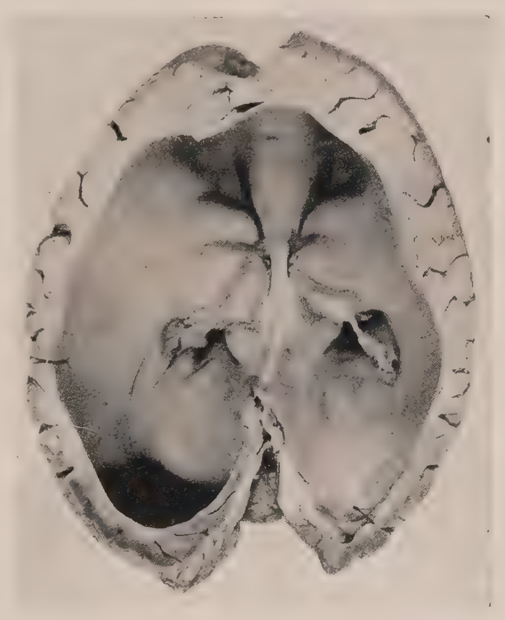
FIG. 457.—Section of Brain in congenital Hydrocephalus, showing enormous dilatation of the Ventricles.

The etiology of congenital hydrocephalus is not yet fully understood, but recent observations show that as a rule, at least, it is brought about in the same way as the acquired form. The application of cerebral pneumography and other methods, as just explained, has now demonstrated that cases of congenital hydrocephalus are really obstructure in nature, and all the types above described have been met with. In some cases closure or atresia of the aqueduct has been found, there being of course dilatation of the lateral and third ventricles. Dandy found the lesion to be in this position in 50 per cent. of cases of congenital hydrocephalus. In others the foramina of Luschka and Magendie have been closed as the result either of defective formation or of intra-uterine meningitis. And in this form the fourth ventricle is usually dilated, sometimes to a great degree, and the distension is occasionally accompanied by abnormalities in the adjacent parts of the cerebellum. In others again there has been thickening of the pia-arachnoid with obliteration of the cisterns at the base or of the subarachnoid space beyond. It is to be noted that congenital hydrocephalus is not infrequently associated with spina befida. The latter condition may result from the distension of the spinal subarachnoid space interfering with the closing-in of the spinal canal posteriorly.

INFLAMMATORY CHANGES

1. Meningitis

Pachymeningitis. Acute inflammation of the dura is practically always due to an extension of septic inflammation from the bones of the skull. It is met with most frequently as a result of chronic middle ear or mastoid disease, occasionally in disease of the nasal bones. It may occur also as a result of compound fracture, as can be readily understood. When pyogenic organisms spread to the dura from the bone, suppurative inflammation occurs in the former, and there may be accumulation of pus underneath it. Its substance becomes swollen, softened and infiltrated with pus, and is often discoloured in appearance. The inner aspect of the dura becomes inflamed and the organisms may infect the arachnoid, setting up either localised or general leptomeningitis. Further effects, such as the production of cerebral abscess, are described below. When the disease of bone is of chronic nature much thickening of the dura in relation to it may occur. The dura is not infrequently the site of gummatous lesions in syphilis (p. 755), but it is rarely affected by tubercle except in the case of direct spread, for example, from the petrous bone or vertebral column.

(The so-called pachymeningitis hæmorrhagica has already been described (p. 721)).

Leptomeningitis. This condition is essentially due to the spread of micro-organisms in the subarachnoid meshwork. When the organisms reach this situation they set up an inflammatory change, and thus lymph is added to the cerebro-spinal fluid, producing a medium in which they can multiply freely. Owing to the wide intercommunicating system beneath the arachnoid, they readily spread, and in this they no doubt are aided by the normal movements of the cerebro-spinal fluid. The exudate is most abundant where the arachnoid is loosest, and thus tends to accumulate in the cisterns at the base of the brain. In most cases the exudate is in the subarachnoid space as already described, so that it cannot be scraped off ; but in severe, especially purulent cases, there may be extension to the subdural space.

Causes and Modes of Infection. The commonest causes of leptomeningitis are the ordinary pyococci, pneumococcus, meningococcus and the tubercle bacillus ; less frequent causal agents are bacilli of the coli-typhoid group, influenza bacillus, gonococcus, anthrax bacillus, streptothrices, etc. In some cases the bacilli reach the leptomeninges from an adjacent infection, in others the infection is by means of the blood stream. (*a*) As examples of the former may be mentioned septic inflammations of the bones and dura, which may result from compound fractures or from such conditions as middle ear disease, suppurative infection of the nasal bones or of the frontal sinuses, etc. The spread may take place in such instances directly through the dura or along a nerve, e.g. the auditory nerve in middle ear disease; or again it may spread along an emergent vein, from the bone to a sinus and thence to the meninges, with or without the formation of abscess in the brain. In young children, pneumococci may spread by the Eustachian tube to the middle ear, giving rise to acute otitis media, and thence to the brain; this is the usual sequence of events in cases of pneumococcic meningitis in early life. Infection may occur also secondarily to disease of the ethmoidal cells. Pneumococci of Group IV are the ordinary causal agents. It may be added that acute leptomeningitis is sometimes met with in cases of simple fracture of the skull, and is apparently the result of direct extension from the sinuses or roof of the pharynx of organisms to the membranes.

(*b*) Spread by means of the blood stream is seen in cases of suppurative inflammation elsewhere, in septicæmia, bacterial endocarditis, pneumonia, fevers, etc. In acute staphylococcus infections, for example in suppurative osteomyelitis, the infection of the meninges sometimes occurs from a small abscess in the cerebral cortex. In the case of cerebro-spinal fever, the evidence points to a passage of the meningococci from the nasopharynx to the meninges by means of the blood stream. In connection with this, the fact that there are cases of meningococcic septicæmia without any meningitis, is of considerable importance. Further, cases of primary pneumococcic meningitis in the adult without other discoverable lesion are met with, and here also the infection is evidently blood-borne. The commonest causes of acute leptomeningitis appearing as a *primary* disease, are the meningococcus and pneumococcus. It may be added that tuberculous meningitis may be relatively acute and may appear as a primary condition.

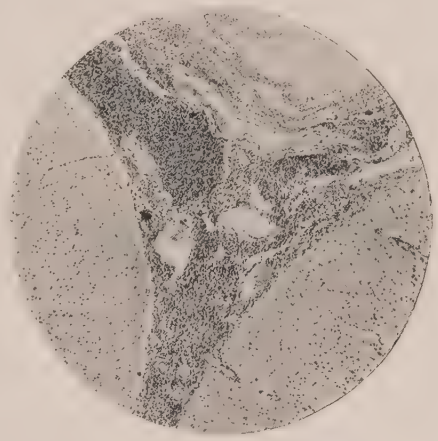

Fig. 458.—Section of Cerebral Cortex from a case of Acute Meningitis due to Pneumococcus, showing distension of the subarachnoid space with polymorpho-nuclear leucocytes. × 30.

Structural Changes. As already stated, the exudate occurs in the meshwork of the arachnoid and tends to be most marked where the spaces are largest (Fig. 458). Thus it is most abundant along the sulci, where it obscures the blood vessels to a varying degree, and at the base of the brain, where it accumulates round the optic chiasma and in adjacent parts. It varies markedly in character, even in the same type of infection. There may be merely excess of fluid of turbid appearance along the sulci, the exudate may be abundant and yellowish and have a tough consistence owing to its fibrinous character, or again, it may be distinctly purulent in type. Not infrequently the ventricles become implicated and contain turbid fluid, whilst a varying amount of exudate is present on their walls. Internal hydrocephalus is a common result. In anthrax infection of the meninges, the exudate is serous and contains a considerable admixture of blood. In fact the effused blood may be so abundant as to simulate diffuse subarachnoid hæmorrhage.

In all varieties of cerebral meningitis the *spinal meninges* become involved in a varying degree. This is readily intelligible in view of the direct continuity of the cerebral and spinal subarachnoid spaces. The latter, which is of large size, becomes distended in cases of meningitis, and when lumbar puncture is made for purposes of diagnosis, the cerebro-spinal fluid is often found to be under considerable pressure. The fluid thus drawn off presents varying degrees of turbidity up to a distinctly purulent condition, and on microscopic examination in acute cases is found to contain chiefly polymorpho-nuclear leucocytes. The causal organisms are often to be seen, although in some cases they can be obtained only by culture. On post-mortem examination the appearances of the cord correspond in their general features with those described above. Fibrinous or purulent exudation when present is usually most abundant over the posterior aspect, and may obscure the vessels to a considerable extent.

In the epidemic form of meningitis or *cerebro-spinal fever* great variations in the intensity of the inflammation are met with. The exudate may be abundant, and then it has a yellowish and almost purulent appearance, or on the other hand it may be only a turbid serous fluid. The brain and cord are usually both affected, though in an unequal manner. Occasionally the ventricles of the brain are chiefly involved ; their walls may be covered by copious exudate, and not infrequently hæmorrhages are present in them and in the surrounding brain substance. It is to be noted that while, as a rule, meningococci can be readily found in the exudate and cerebro-spinal fluid, most being contained within the polymorpho-nuclear leucocytes, in some cases, especially those of less severe degree, they are very scanty and may not be found on microscopic examination. In this type of meningitis, extensive phagocytosis of the polymorpho-nuclear leucocytes by macrophages is often a striking feature in the exudate in the membranes. In cases which are not fatal within a short time the disease often passes into subacute and chronic stages, and then important structural changes follow. The soft membranes become thickened and œdematous, and various cranial nerves are involved so that paralyses result. The foramina in the roof of the fourth ventricle become implicated, and this, along with obliteration of the subarachnoid space at places, interferes with the normal flow of the cerebro-spinal fluid. Thus marked hydrocephalus results and is often the cause of the fatal issue. Similar chronic changes occur in the spinal meninges and there may be some involvement of the superficial parts of the cord as well as the roots of the nerves.

The term *posterior basal meningitis* is applied to a variety which is not uncommon in young children. The acute stage is generally mild but subacute or chronic lesions are common; the changes are rather thickening and œdema of the membranes than fibrinous exudate. As the name implies, the parts in the posterior fossa are specially affected, and hydrocephalus is often produced by implication of the roof of the fourth ventricle. The causal organism, which is usually scanty and difficult to find, has the microscopical and cultural characters of the meningococcus, and is probably to be regarded as a variety of that organism.

Benign Lymphocytic Meningitis. This seems the most appropriate name for a condition which has been recently recognised as a virus infection. It is also known as 'serous meningitis.' The disease chiefly affects children and is of mild nature as a rule. There may be various symptoms of spinal irritation, such as nuchal rigidity; there may also be some pyrexia. The cerebro-spinal fluid is under some increased pressure and contains an increased number of lymphocytes with slight increase of protein. The infection has been transmitted to monkeys and mice and can be maintained in them indefinitely in series. Immunological reactions show that it is distinct from other virus infections.

2. Encephalitis

We shall first of all give a general account of the inflammatory conditions affecting the brain substance and afterwards consider some of the more important examples.

Acute Encephalitis. 1. Virus Infections. Recent work has shown that bacteria play a relatively small part in the production of acute encephalitis and that in the great majority of cases the causal agent is a virus. Certain filter-passing organisms or viruses have a special affinity for the nervous system and they often become diffusely distributed throughout it. Thus, two well recognised infections of the nervous system, encephalitis lethargica and acute anterior poliomyelitis, are virus diseases which have been extensively investigated. Hydrophobia belongs to the same group, though inflammatory changes are less in evidence. Within recent years other forms of encephalitis and myelitis with characteristic changes have been met with as a sequel to various infections, and the relation of these has not yet been fully determined. There are also other types of acute inflammation of the central nervous system which occur apart from any previous infections. Some facts with regard to these will be given below.

Levaditi has pointed out that the diseases mentioned, to which vaccinia may be added, constitute a group in which the viruses are characterised by a marked affinity for structures derived from the ectoderm. He has thus applied the term *ectodermoses* to such infections, and distinguishes a *neurotropic* and a *dermotropic* type according to the relative affinity for the nervous system and the skin structures respectively. It may be added that the affinity of a virus for tissues may be altered by inoculation methods. Thus a strain of the vaccinia virus called *neuro-vaccine* which produces lesions in the central nervous system in rabbits has been obtained.

The differentiation of such diseases is attended with considerable difficulty. None of the viruses concerned in encephalitis have been cultivated outside the body apart from living cells, and only in some instances has the infection been definitely transmitted to the lower animals. The recognition of different diseases thus rests mainly on their conditions of occurrence and clinical features, and on the characters and distribution of the lesions, which vary greatly. Sometimes there is actual softening of the nervous tissue—*inflammatory softening*. One group is characterised by the rapidity with which *demyelination* or disappearance of the medullary sheaths occurs ; this is a histological change which offers a contrast to the lesions in other infections, notably encephalitis lethargica and anterior poliomyelitis. It may be added that in the case of none of the demyelinating affections has it yet been possible to transmit the disease to the lower animals.

A feature of special interest is that in many instances it has been demonstrated that the virus may spread along the nerves either to the periphery from the brain or in the opposite direction. It has long been known that the virus of rabies spreads in this way and also the virus of poliomyelitis, but the extent to which a virus may become disseminated has been shown only in recent times.

We shall now give an account of the chief non-bacterial infections.

Encephalitis Lethargica or Epidemic Encephalitis. This affection is the best example of an acute non-suppurative inflammation of the brain substance. It has occurred in epidemics in various parts of the country, though there are comparatively few instances of its passing directly from one person to another, and the mode of infection is not fully known. The symptoms indicate a *general* affection of the brain—pyrexia, drowsiness and delirium being present ; there is usually a general weakness of muscular power, along with more or less lethargy, hence the name originally applied. In addition, there may be *local* symptoms due to implication of the oculo-motor, facial, and other nerves, and sometimes there is nystagmus.

The mortality varies in different epidemics, but may be said to be on the average about 25 per cent. Amongst the non-fatal cases, however, residual symptoms more or less permanent occur in a considerable proportion. A group of these symptoms, or a syndrome, including tremor, rigidity and loss of associated movements, is described as of the Parkinsonian type owing to a resemblance to paralysis agitans which was first described by Parkinson. Immobile facial expression is of common occurrence, as are also emotional disturbances of various kinds, excessive salivation, etc. Very noteworthy, especially in children, is a loss of moral sense with a tendency to violent actions.

The Structural Changes are of a definite kind. *Post mortem*, at the acute stage there is usually a marked congestion of the leptomeninges, especially over the pons and medulla and lower parts of the brain, and occasionally minute hæmorrhages are present. Intense congestion is to be found throughout the substance in the parts mentioned, and here also, minute hæmorrhages and even points of softening may be present. In some cases the naked-eye changes are of a distinct character, but in others they may be comparatively little marked, especially at a later period of the disease. They are often noteworthy in the region of the floor of the fourth ventricle.

Microscopic Examination shows that the lesion is of acute inflammatory character with damage to the nervous elements, although the changes present in any case depend upon its duration and severity. In very severe cases, with death at an early period, damage to the vessels and the nerve cells is the outstanding feature; but leucocytic emigration soon occurs and in less acute cases comes to be of marked degree. The effects on the blood vessels are shown by the intense congestion, by hæmorrhages both into their sheaths and into the tissues around, and sometimes by actual thrombosis; occasionally part of a vessel wall may appear swollen and hyaline, as if it were becoming necrotic (Fig. 459). Many nerve cells show chromatolysis and other signs of degeneration, and some may be seen in process of being attacked by phagocytes; and it has been shown that many nerve cells may be destroyed. The leucocytes which are present are chiefly lymphocytes along with a few plasma cells, and they appear first of all around the blood vessels, especially the minute venules; accumulation of these cells increases as time goes on, and ultimately they may form distinct sheaths to the vessels (Fig. 460). They occur also around the capillaries and are sometimes diffusely arranged in the intervening tissues. The neuroglial tissue may show loss of outline and signs of softening, whilst in the less acute cases neuroglial overgrowth and thickening may be present. Although such changes are most frequently met with in the pons and medulla,

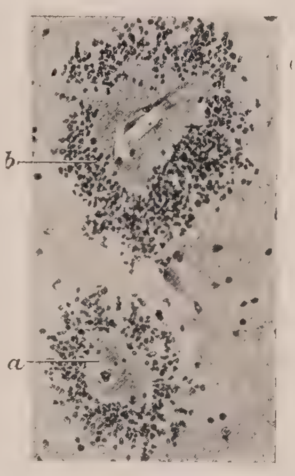

Fig. 459.—Encephalitis Lethargica in early acute stage, showing (*a*) hyaline swelling in and around walls of Blood Vessels; (*b*) extravasation of red Corpuscles. × 170.

they have been found also at higher levels, for example in the basal ganglia and in the cortex. It may be noted that infiltration of cells similar to those described occurs in the soft membranes.

The cerebro-spinal fluid may be quite normal but usually there is a lymphocytosis of 10–100 or even more cells per c.mm. As a rule, polymorpho-nuclear leucocytes are absent but a few have been found in a small proportion of cases. An increase of the cells is not usually accompanied by any distinct change in the total protein or in the globulin. This is an example of the so-called cell-protein dissociation, the opposite condition, increase of globulin without increase of cells, being found in the Nonne's compression syndrome. The Lange colloidal gold test as a rule gives some reaction, usually a curve of the luetic type but sometimes of the paretic type (Greenfield).

The histological changes which have been often associated with Parkinsonism are chiefly centred in the substantia nigra in the crura cerebri and may have relation to the bilateral rigidity which is often present (McAlpine). They consist in disappearance of a considerable proportion of nerve cells, with chromatophilic and other degenerative changes in some of those surviving, increase of neuroglia with new formation of vessels; perivascular infiltration of leucocytes may still be present. The changes suggest that they are not merely the result of damage done in the acute stage but that they are due to a persistence of the virus in the tissue of the brain. Changes in adjacent parts, e.g. the lentiform nucleus, have been met with but they have been irregular in their distribution and slight in degree. The lesions in the substantia nigra are supposed to interrupt fibres from the nucleus pallidus which pass directly or through other centres to the lower motor neurons in the spinal cord. This results in the loss of the inhibiting and controlling influence on movement, and thus the rigidity which is a characteristic feature of the disease results. In this respect there is an analogy to what is seen in lenticulate degeneration (p. 717).

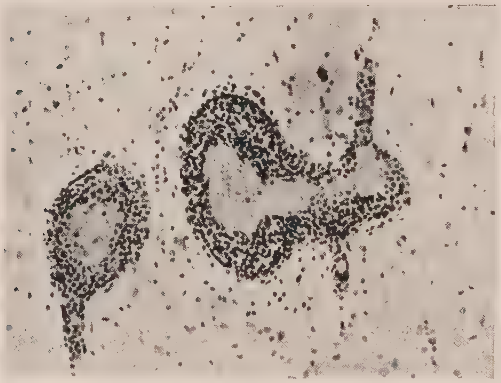

Fig. 460.—Section of posterior part of Medulla in Encephalitis Lethargica, showing the extensive perivascular Infiltration of Lymphocytes and Plasma Cells. × 170.

In the affected tissues no definite organisms of any kind have been found on microscopic examination. Da Fano has demonstrated the presence of minute bodies which occur especially within the nerve cells, though also outside, occasionally within leucocytes. They appear as small granules which stain metachromatically with polychrome blue, and most of them are surrounded by light areas or halos; they are occasionally arranged in pairs. It is not clear whether they represent parasites in some form or whether they are derivatives of the tissue elements. Several observers have described the transmission of the disease to rabbits and monkeys by intracerebral inoculation. In most cases, however, attempts to transmit the disease to animals have failed, and some of the positive results described may have been due to the virus of herpes which has a wide distribution in animals. There is no satisfactory evidence that the virus has been successfully cultivated outside the body, though announcements have been made to this effect.

It is now clear that encephalitis lethargica is only one of a group of virus infections of the nervous system in man and the lower animals, and several others have now been described and differentiated. One or two of the chief of these may be briefly referred to.

St. Louis encephalitis, called after the place of its occurrence in 1933, presented many resemblances to encephalitis lethargica. It was a relatively fatal disease, tending to affect adults especially, and was not followed by Parkinsonism. It was found to be readily transmissible to monkeys and mice and could be maintained in them in series. Immunological reactions showed that it was distinct from other known infections. Other examples of infections of similar though distinct nature are, a form of encephalitis which occurred in Australia and is known as *Australian X-disease,* and *Japanese encephalitis.* Benigh lymphocytic meningitis (p. 739) is another virus infection of the central nervous system. In the lower animals *Borna disease* in horses and *louping-ill* in sheep are examples of virus diseases.

Post-infectional Encephalitis. This term may be provisionally applied to encephalitis occurring after various infections, as the relation of the viruses concerned is still undetermined. Within recent years quite a number of cases of encephalitis have occurred after vaccination both in this country and on the continent—*post-vaccinal encephalitis.* The cases have been amongst children and young adults and the onset of the disease has usually been about ten days after vaccination. The lesions are of the focal type, occurring mainly around the small arteries and are widely distributed both in the brain and in the spinal cord; and corresponding symptoms result. There is a certain amount of leucocytic infiltration both in the perivascular space and also in the tissues around, the cells being chiefly of the non-granular type. But the characteristic feature is the loss of myelin from the medullated fibres in the zones around the vessels (Fig. 461). This process of demyelination takes place with great rapidity, being sometimes almost complete within four days. In this respect there is a contrast to the demyelination met with in Wallerian degeneration which takes weeks to occur. The rapid demyelination in post-vaccinal encephalitis indicates the presence of some lytic agency, but the nature of this is unknown. Two chief views have been held with regard to the significance of the encephalitis. One is that the lesions are produced by the vaccinia virus; the other is that the lesions result from a secondary infection with a virus whose nature is unknown.

Cases of encephalitis of similar nature have been observed after measles and influenza (Greenfield), smallpox and antirabic inoculation, and it is a striking fact that in these the histological changes have been of the same nature as those in post-vaccinal encephalitis. On the other hand the lesions are quite different, both in character and in distribution, from those in epidemic encephalitis and also from those which are produced in the rabbit by the vaccinia virus. In view of these facts the opinion has been adopted by some writers that the demyelinating type of encephalo-myelitis is a definite disease produced by one virus and that the various infections after which it occurs act as favourable conditions for the entrance of the virus. It may be mentioned, however, that in one case of post-vaccinal encephalitis a virus was obtained which produced the lesions of vaccinia on inoculation (Turnbull and Mackintosh). There is just the possibility, however, that this virus may have been present in the nervous system as the result of vaccination, although not the cause of the typical encephalitis. At present one is not justified in coming to any conclusion with regard to the relation and significance of post-infective encephalitis. The condition is known also as *acute disseminated encephalo-myelitis.*

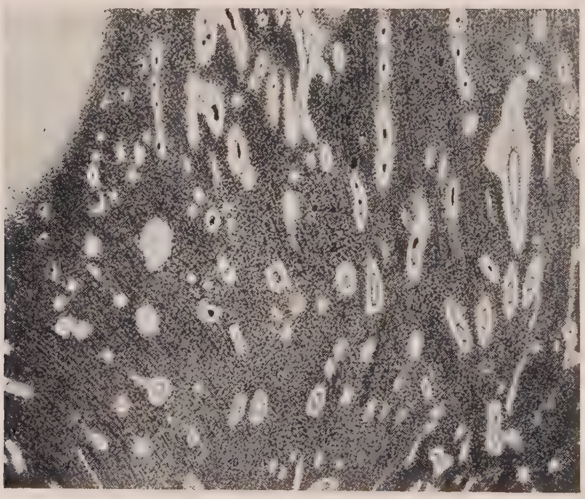

Fig. 461.—Section of Brain from a case of Post-Vaccinal Encephalitis, showing areas of demyelination around blood-vessels. (Dr. J. R. Perdrau.)

Demyelination of subacute type has been observed in dogs suffering from canine distemper and also apart from this infection. There is no evidence that it is caused by the virus of distemper (Perdrau and Pugh). The occurrence of such a condition is of special interest as it occupies an intermediate position between the forms of acute demyelinating encephalitis and the chronic conditions of multiple sclerosis and Schilder's disease.

In fatal cases of *typhus fever* cerebral lesions in the form of focal encephalitis are usually present; they are of nature similar to those in other parts of the body. They are commonest in the medulla and pons but are also widely distributed especially in the grey matter, and are the result of the virus (*Rickettsia*) settling in the capillary endothelium. Thrombosis within the affected capillaries and endothelial proliferation then occur, whilst around there is an active enlargement and proliferation of the mesoglial cells. Polymorphonuclear leucocytes and other cells also take part in the reaction. The result is the formation of a minute tubercle-like, cellular nodule. Nerve cells in the vicinity may be involved and become the prey of phagocytes. These focal lesions are often very numerous and no doubt play an important part in producing cerebral symptoms and in leading to a fatal result.

Wernicke's Encephalitis or Poliencephalitis Hæmorrhagica Superior. This is a condition with definite features. It is a symmetrical affection of the grey matter round the third ventricle, hypothalamus and medial portions of thalami, and round the aqueduct of Sylvius; to a less extent in the floor of the fourth ventricle. The affected parts show marked congestion and numerous small petechial hæmorrhages, which mark them off from the normal tissue. The microscopic changes are chiefly vascular—marked irregular dilatation of capillaries and vessels a little larger, with escape of red corpuscles. The parenchyma is œdematous but there is relatively little damage to nerve cells. There is microglial reaction with formation of compound granular corpuscles and later there is neuroglial increase. Emigration of leucocytes from the blood is little marked.

The associated symptoms are both general and focal. There are usually depression and drowsiness passing into coma; sometimes there is excitement. The focal symptoms are chiefly related to the eye muscles—ophthalmoplegias and nystagmus.

Nothing definite is known as to etiology. The early view that the condition was mainly due to chronic alcoholism has not been supported by further observations. The condition occurs as a complication of various diseases, in a considerable proportion of which the stomach is involved, e.g. gastric carcinoma, but whether it is of infective or deficiency nature cannot be stated.

Rabies or Hydrophobia. In this disease, also due to a filter-passing virus, changes occur in the nervous system of corresponding nature to those in epidemic encephalitis but of less degree. The virus passes along the nerves from the primary lesion, usually a bite, to the central nervous system. The histological changes, which are specially marked in the nuclei of the medulla, though occurring also in other parts, consist in capillary congestion with small hæmorrhages, chromatolysis and other degenerative changes in the nerve cells, and a certain amount of perivascular lymphocytic infiltration. The most characteristic feature, however, is the presence of peculiar structures called 'Negri bodies' within the protoplasm of nerve cells and their processes. Although met with in all parts of the brain they are specially abundant in the cells of the hippocampus major or cornu

Ammonis and the Purkinje cells of the cerebellum, and can be readily found in smear preparations from these parts. They vary greatly in size, measuring 0·5–25 μ, and are rounded, oval or somewhat angular in form. They are composed of a homogeneous substance in which small round or oval bodies or granulations are present. In preparations coloured by Giemsa's stain or by eosin-methylene-blue, the bodies are coloured in varying tints but have on the whole an affinity for eosin. The nerve cells affected may otherwise appear comparatively healthy. Opinion still varies regarding the nature of the Negri bodies. One view is that they represent products of reaction or of degeneration around the virus within the nerve cells. Another put forward more recently is that they really consist of masses or aggregates of minute 'elementary corpuscles' representing the virus. The important practical point is that they are specific to rabies.

Encephalitis Periaxialis Diffusa. This condition, which occurs in the early years of life, was first described by Schilder in 1912, and since that time a considerable number of cases have been recorded. It is characterised by the occurrence of extensive areas of degeneration in the central white matter of the hemispheres and in its general features has certain points of resemblance to multiple sclerosis (p. 781). The myelin sheaths of the nerve fibres become degenerated and undergo absorption, and this process of demyelination may occur over a wide area. The axis cylinders also become affected and many disappear later, so that, unlike what occurs in multiple sclerosis, secondary Wallerian degeneration in nerve tracts is common. Along with these changes the affected area is infiltrated to a varying extent by round cells chiefly of neuroglial origin, and some of these act as phagocytes. There are also present larger cells containing several nuclei situated peripherally—the so-called 'globoid cells.' There may be also considerable perivascular infiltration of lymphocytes. It would appear, however, that the process of demyelination is the essential change. The affected tissue becomes greyish in colour owing to loss of myelin, and also somewhat shrunken. The disease usually starts in the white matter of the occipital lobes and spreads forwards and downwards by continuity, though also discontinuously. Both lobes are affected as a rule. The white matter of the occipital and temporal lobes may be largely replaced by grey tissue, and islets of the same may be present in other parts. The cortical grey matter and the subcortical arcuate fibres are spared to a large extent. Owing to the extensive implication of the optic radiation in the occipital lobes, cerebral blindness is a prominent early symptom and deafness also may result from involvement of the temporal lobes. Interference with the mental faculties and spastic paralysis may also be present. The disease, which is also known as *diffuse cerebral sclerosis*, sometimes runs a relatively acute course. Nothing is as yet known with regard to its etiology.

2. **Bacterial Encephalitis.** This may be *suppurative* or *non-suppurative* in character. The former is due to the ordinary pyogenic organisms which may spread from some lesion in the vicinity, or may be carried to the brain by the blood stream ; it will be conveniently described by itself. Non-suppurative encephalitis likewise may result from extension of inflammation, usually from the meninges, or by blood infection.

With regard to extension from *acute meningitis*, it may be said that the superficial parts of the cortex are probably always affected to some extent, and in this way symptoms of cerebral irritation are produced. The degree to which this occurs, however, varies greatly. In some cases it is striking how little leucocytic infiltration may be present along the blood vessels; in others the perivascular spaces are crowded with leucocytes which may extend a considerable distance into the brain substance, whilst exudate, hæmorrhage, and a certain amount of cortical softening may be present. In tuberculous meningitis there is usually marked involvement of the cortex, many of the small vessels may be thrombosed or obliterated, and a considerable amount of hæmorrhage and softening of the grey matter may result. A similar statement applies to lesions of the spinal cord.

The softening which occurs around gross lesions in the brain is mainly the result of local anæmia and œdema brought about by pressure, tumours, etc., and should not be described as inflammatory, although this term is often used. In the case of cerebral abscess, however, softening is occasionally met with for a considerable distance around, and this is produced by the diffusion of toxins which act directly on the brain substance and cause an inflammatory œdema.

A form of acute hæmorrhagic encephalitis in which the chief lesion consists in multiple minute hæmorrhages throughout the brain substance, has occasionally been met with in syphilitics after treatment with salvarsan and also in other conditions. Its exact nature is obscure.

Suppurative Encephalitis—Cerebral Abscess. As in the cases of other organs, infection of the brain by pyogenic organisms may occur by direct spread from lesions in the vicinity, or it may take place by means of the blood stream.

(1) DIRECT EXTENSION OF ORGANISMS. This is seen in two main conditions, namely: (*a*) Carious disease of the bones of the skull, and (*b*) compound fracture with septic inflammation. Thus chronic middle ear or mastoid disease, and corresponding affections of the ethmoid and nasal bones and frontal sinuses, may lead to cerebral suppuration. In most cases direct extension can be traced. The carious process reaches the dura and produces a local pachymeningitis, the dura becomes swollen, discoloured, and infiltrated by pus, and there is often accumulation of pus between it and the bone. The inflammation extends to the soft membranes, and may be limited by adhesions, or, on the other hand, a diffuse leptomeningitis may be set up. In the former case the organisms cause a superficial destruction of the cortex, or ulcer of the brain, and then may spread deeply into the brain substance, where an abscess of considerable size may be produced, which is often of chronic character. A closely similar sequence of events occurs in cases of compound fracture. In many cases of bone disease the abscess is separated from the surface by a layer of healthy brain substance, and no path of infection can be traced with the naked eye; in fact, sometimes in middle ear disease

the caries may not have reached the surface of the bone. In such cases extension takes place by the blood vessels, either within a vein or by the perivascular tissue. In connection with this it is to be noted that the emergent veins from the bone drain into a venous sinus, into which the veins of the brain also discharge, and in this way a path of infection is provided. It is of course evident that the existence of septic thrombus in the particular sinus will aid the spread of infection, but an isolated cerebral abscess often occurs apart from sinus thrombosis.

By far the commonest cause of *cerebral abscess* is carious disease of the middle ear and mastoid antrum, and the commonest sites are the temporo-sphenoidal lobe and the cerebellum, the former being the more frequent. If the middle ear disease spreads upwards through the tegmen tympani, and reaches the anterior surface of the petrous, it comes into relation with the under surface of the temporo-sphenoidal lobe, and thus the abscess occurs in this lobe (Fig. 462). If, on the other hand, the disease has spread from the mastoid antrum, or from the middle ear to the posterior aspect of the petrous, the abscess occurs in the cerebellum ; and in such cases the sigmoid sinus often becomes implicated and is the seat of thrombosis. A chronic temporo-sphenoidal abscess may be of considerable size ; it is usually of oval shape, conforming to that of the lobe, and may measure two or three inches in length ; occasionally it is somewhat loculated. In the cerebellum a considerable part of a lateral lobe may be occupied by the abscess, which usually comes close to or reaches the anterior border, the lobe often being adherent to the bone at that point.

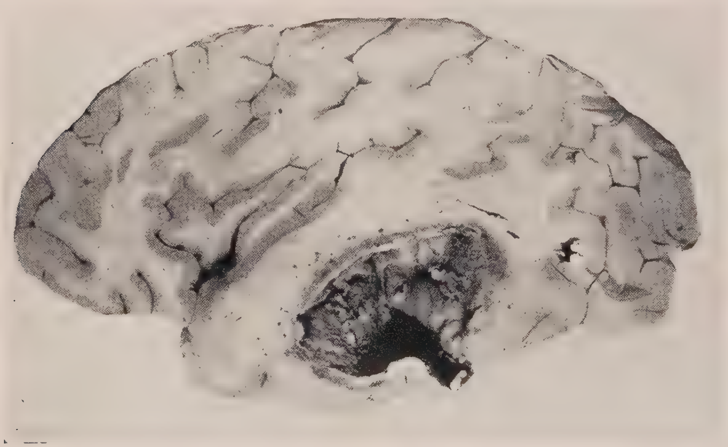
FIG. 462.—Longitudinal section of Brain, showing chronic Abscess in Temporosphenoidal Lobe.

The contents of a chronic cerebral abscess are usually a thick greenish-yellow pus with foul odour, and as a rule there are a large number of bacteria of different kinds—the ordinary pyococci and various bacilli. The wall of the cavity consists mainly of young connective tissue and new blood vessels, that is, of ordinary granulation tissue. Externally to the newly formed tissue blends with proliferated neuroglia and the glial thickening gradually fades off at the periphery. In many cases a cerebral abscess may exist for a considerable time in a comparatively latent condition, but more acute symptoms may develop, owing to the spread of the suppuration and sometimes as a result of acute inflammatory œdema and swelling of the parts around. Sometimes, again, the organisms spread to the meninges and produce an acute leptomeningitis.

Abscess in the temporo-sphenoidal lobe or in the cerebellum is, as we have said, caused by *disease of the middle ear* or of the mastoid antrum and air cells. This disease is the result of an ascending inflammation by the Eustachian tube from the pharynx, such an occurrence taking place especially in children, though met with also in adults. Not infrequently, it starts in connection with one of the specific fevers, notably scarlet fever; and the organisms chiefly concerned are streptococci and pneumococci, but a variety of others become superadded. At first there is set up an acute inflammation of the lining of the tympanic cavity, etc., with purulent discharge, and if this continues, the lining membrane becomes destroyed and replaced by a layer of granulation tissue; very frequently, though not invariably, perforation of the tympanic membrane results. The bone often becomes involved in a carious process which destroys the various structures and may reach the dura, giving rise to one or more of the various lesions mentioned—local meningitis, erosion of the brain, acute leptomeningitis, cerebral abscess, sinus thrombosis, etc. And just as an abscess may occur by extension of the organisms along blood vessels before the dura has been involved, so also an acute leptomeningitis may be set up by the spread of organisms along the sheath of a nerve, especially the auditory.

Sinus Thrombosis. This is the result of an extension of septic inflammation to the wall of a sinus, and occurs most frequently in the sigmoid sinus in cases of mastoid or middle ear disease. The first effect is the production of acute phlebitis with secondary formation of thrombus on the damaged intima. At the very earliest period the thrombus may be free from organisms, but it soon becomes invaded by them and then suppurative softening of its substance occurs. When once thrombosis has started it tends to spread, and it may pass into the internal jugular vein. The oldest part of the thrombus thus comes to be occupied by purulent material, while the process of ordinary thrombosis continues to spread at the end, and thus may prevent the detachment of infected portions. We have in this way an explanation of the fact that while septic emboli may become detached, and cause secondary abscesses in the lungs, this occurs only in a relatively small proportion of cases of septic sinus thrombosis.

(2) Infection by the Blood. Abscesses in the brain caused by septic embolism used to be not uncommon in cases of surgical pyæmia in pre-antiseptic days; they are now relatively rare and are chiefly secondary to lesions in the lungs, such as abscess, bronchiectasis, or gangrene, and are the result of septic involvement of small veins with subsequent embolism. They are not infrequently multiple, and vary greatly in size. Small foci of suppuration may be met with in acute pyogenic infections, e.g. suppurative osteomyelitis, bacterial endocarditis, etc. They are often quite minute, and may appear rather as hæmorrhagic points, their true nature being revealed on microscopic examination, by means of which small plugged vessels may be seen in their central parts. Such lesions may be produced by cocci in the blood settling in the capillary endothelium, as well as by actual embolism.

We may add that abscesses in the brain, single or multiple, and sometimes of considerable size, may occasionally be produced by the *actimomyces* and other streptothrix organisms; they usually occur secondarily to similar lesions in the lungs.

SPECIFIC INFLAMMATIONS

Tuberculosis. The central nervous system is comparatively often the seat of tuberculous disease, which occurs in two main forms. The commoner is an affection of the leptomeninges, in which disseminated tubercles form and lead to inflammatory change—tuberculous meningitis. In the less common affection, tubercle nodules of considerable size, single or multiple, form in certain parts of the brain substance, and their effects often correspond with those of tumour growth.

Tuberculous Meningitis. In this affection we have an example of inflammation with exudation associated with the presence of tubercles in the leptomeninges. The bacilli may reach the membranes by means of the blood stream during the course of a generalised miliary tuberculosis, or by direct spread from tuberculous disease in any of the bones related to the central nervous system (*e.g.* petrous or vertebrae) or by lymphatics from some lesion in the thorax or abdomen. Another mode of infection is from small caseous lesions which are most frequently situated near the surface of the brain. They are often multiple and may contain abundant tubercle bacilli. Such lesions are quite distinct from the large encapsulated tuberculomata. According to Rich and McCordock it is from such small foci, which are secondary to tuberculous disease in the respiratory or alimentary system, that tuberculous meningitis most frequently takes origin. They consider, both on morphological and experimental grounds, that tuberculous meningitis is not the immediate result of hæmatogenous infection of the meninges, but is due to discharge of large numbers of tubercle bacilli into the sub-arachnoid space from these pre-existent caseous foci. It is, however, difficult to apply this view generally to cases where meningitis is associated with a general miliary tuberculosis and also the presence of tubercles in the choroid plexuses, as frequently occurs.

STRUCTURAL CHANGES. When the bacilli reach the membranes they have a great tendency to spread in the perivascular connective tissue of the arteries. Here and there they become arrested and produce tubercles, which can be seen as small grey nodules along the lines of the vessels. Apparently by the diffusion of toxins in the subarachnoid space a general effect on the vessels is produced, and inflammatory exudate, often of a fibrinous character, occurs. Leucocyte emigration is abundant not only in the meninges but also around the nutrient twigs as they extend into the brain substance. The leucocytes are for the most part of the lymphocyte class, but a considerable number of polymorpho-nuclears are present also. The tubercles in the meninges are rounded aggregations of cells with caseation in their centre rather than typical follicles; and giant-cells are usually not a prominent feature, though they may be present. Necrosis and caseation affect also the cells in the exudate, so that in certain areas both fibrin and cells are stained alike. Another important change occurs in the small arteries. The presence of a tubercle on the wall of an artery causes a reactive endarteritis, which leads to great thickening of the intima and not infrequently actual closure; caseous necrosis of the wall may follow. A considerable amount of softening of the superficial grey matter is often present; and this is the result in part of toxic action and in part of the implication of the vessels.

In the great majority of cases the disease starts at the base of the brain and is most marked there (Fig. 463). Occasionally, though rarely, the meningitis is chiefly over the vertex, and again, it may be asymmetrical; for example, there may be a local eruption of tubercles over one hemisphere (Fig. 464). The following are the usual changes to be found *post mortem*. The dura is usually tense, and when it is removed the convolutions are markedly flattened and somewhat dry in appearance. This is the result of accumulation of fluid in the ventricles, which is almost invariably present; hence the disease is sometimes spoken of as *acute hydrocephalus*. The exudate is usually most abundant in the loose arachnoid at the base of the brain; the optic chiasma, anterior surface of the pons, etc., are especially involved and their structure partly obscured. The exudate may be abundant and yellowish, a considerable amount of fibrin being present; and the chief change may be more an inflammatory œdema with greyish opacity and thickening of the membranes. The ventricles are greatly distended with fluid which is often turbid. In adults their walls may be softened, the under portion of the corpus callosum and fornix being specially affected. Tubercles may often be found in the choroid plexuses and also in the lining of the ventricles, and the velum interpositum is often the seat of inflammatory change. On lumbar puncture, in most cases of tuberculous meningitis the cerebro-spinal fluid is found to escape under increased pressure; the hydrocephalus is thus of the communicating type (p. 733). It is mainly due to obliteration of the cisterns at the base of the brain by the inflammatory process, though this is aided by inflammatory changes in the choroid plexuses of the ventricles. In more chronic cases, however, the foramina in the roof of the fourth ventricle may be obliterated by the thickening of the membranes and a non-communicating type of hydrocephalus thus established.

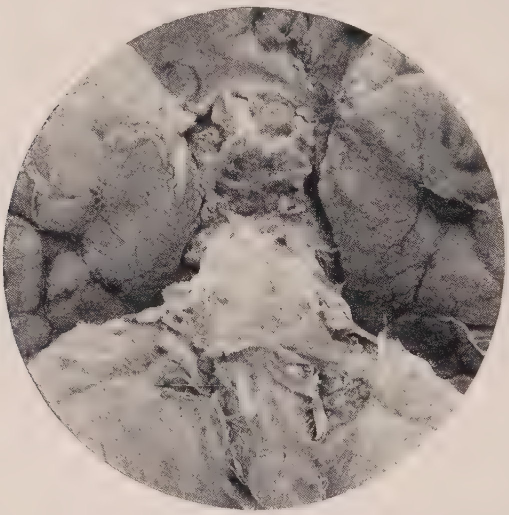
Fig. 463.—Tuberculous Meningitis, showing Exudate at base of Brain, which obscures structures. A few tubercles can be seen in the peripheral parts.

Tubercles are most readily seen in the congested areas just beyond the exudate. A hand lens greatly assists the search for them. Some cases run a relatively chronic course, especially in adults, and in these the chief change is thickening and œdema of the membranes, often with implication of the roof of the fourth ventricle. Tubercles are few and may be found with difficulty; in fact, occasionally the true nature of the case can be determined only by microscopic examination.

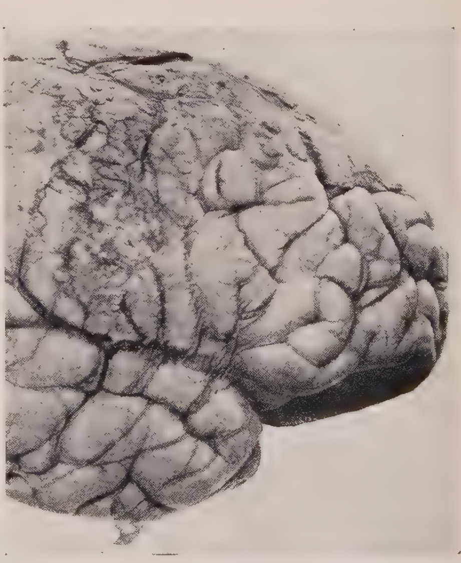
Fig. 464.—Localised Eruption of Tubercle Nodules on surface of Hemisphere in region of Fissure of Sylvius.

The spinal meninges are affected in most cases, and the tubercles have the same characters as, and produce results similar to, those in the brain. Sometimes the affection is most marked in the cervical region, this indicating a downward spread. But sometimes, as has been said, the cord is more affected than the brain, and the appearance of the lesions suggests that the spinal meninges have been primarily involved.

The cerebro-spinal fluid in tuberculous meningitis has usually an opalescent appearance and may give a fine web of fibrin on standing. The number of cells is much raised, often being 200 per c.mm. or even higher; the majority are lymphocytes as a rule, with a small proportion of mononuclears, but polymorpho-nuclears may be quite numerous and may occasionally exceed the lymphocytes, especially in the earliest stages. The polymorpho-nuclears often show signs of degeneration. Tubercle bacilli may be usually found on microscopic examination of the centrifuged deposit or of the fibrin web which forms in the fluid. The protein is increased but in variable amount.

Primary *tuberculosis of the dura mater* is very rare, though occasionally single or multiple chronic nodules may be met with. In tuberculous leptomeningitis, as a rule, the dura mater is quite unaffected. In the case of the spinal cord, secondary infection of the dura mater from tuberculosis of the vertebræ is of common occurrence; in some cases the spinal cord is simply affected in a mechanical way by the angular curvature which takes place, whilst in others the dura may be infiltrated by tubercle and gradually thickened. The process may extend inwards, involving the soft membranes and leading to inflammatory softening of the cord.

THE SYMPTOMATOLOGY of tuberculous meningitis varies greatly as can be readily understood in view of the anatomical changes. The inflammation at the base of the brain leads to implication of various cranial nerves, the oculo-motor being often involved; thus ptosis and various forms of squint and other paralyses are common early symptoms. The affection of the spinal meninges is often evidenced by retraction and rigidity of the neck. The growth of tubercles in the cortex leads to irritation, and when one area is specially affected, as is not uncommon, localised spasms or convulsions may result, whilst the softening of the cortex due to closure of vessels may lead to paralytic symptoms. Lastly, the accumulation of fluid in the ventricles produces the symptoms of general compression of the brain and ultimately coma.

Tuberculous Masses or 'Tuberculomata' (Figs. 465, 466). The occurrence in the brain of tuberculous masses of considerable size, though rarer than tuberculous meningitis, is not uncommon. They are known also as tuberculous tumours, and the term 'solitary tubercle' is sometimes used, though, as a matter of fact, they are not infrequently multiple. They are met with especially in young subjects, and their commonest sites are the cerebellum, medulla, pons and crura; they may occur at a higher level but are comparatively rare in the hemispheres. They are often of about the size of a pea or small cherry, though they may be as large as a walnut or even larger. Unlike gummata, they occur in the brain substance and their distribution is quite irregular. Their consistence is usually firm and they present a dull yellowish centre which is surrounded by a pinkish-grey capsule, though sometimes there may be a considerable degree of vascularity at the periphery. Calcification in a mass has been observed, but is of rare occurrence. Such nodules produce their effects partly by pressure and partly by destruction of nerve nuclei and tracts. When they are in the region of the fourth ventricle or in the pons, they may cause interference with the flow of the cerebro-spinal fluid downwards, and thus give rise to hydrocephalus. Occasionally tuberculous meningitis follows. The charac-

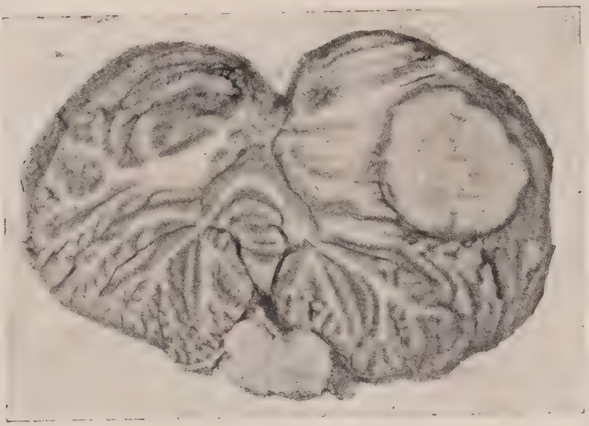

Fig. 465.—Tuberculous Mass in right Lobe of Cerebellum, showing diffuse caseation. × $\frac{2}{3}$.

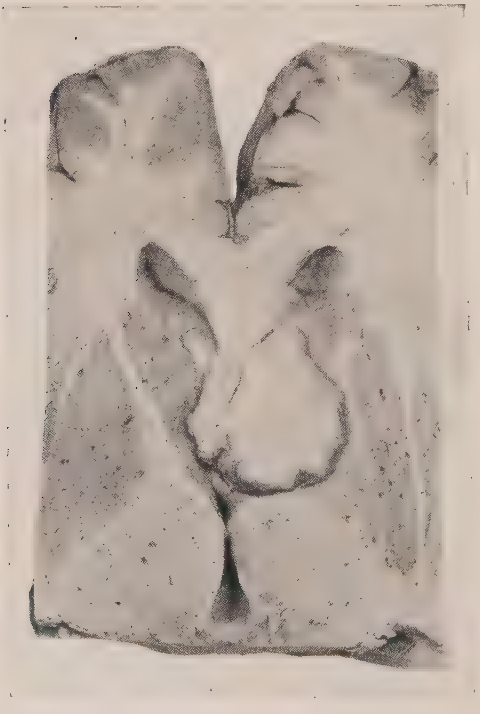

Fig. 466.—Large Tuberculous Mass in the Head of right Caudate Nucleus. × $\frac{2}{3}$.

ters of such tuberculous masses are usually unmistakable, but sometimes the capsular tissue is very abundant, and we have seen cases where the tuberculous mass rather resembled a glioma with some central necrosis.

Syphilis. Syphilitic affections of the central nervous system are of frequent occurrence and lead to manifold serious results. They may be conveniently divided into two groups. (*a*) The first group includes lesions which are found in the late secondary and in the tertiary stages, and which involve the ordinary connective tissues and the blood vessels; the chief forms of this group are meningitis, gummata and endarteritis, and various combinations of these. In this group the lesions are mesodermic. (*b*) In the second group are the important diseases, tabes dorsalis and general paralysis; these occur much later than the tertiary stage and in them the nervous tissue is involved from the outset. Here the lesions represent affections of the neuro-ectoderm.

Syphilitic meningitis may be met with at a relatively early period. It may start in, and affect chiefly, either the dura or the leptomeninges, though not infrequently both are involved together and adhesions are present. Syphilitic leptomeningitis is commonest at the base of the brain, where it causes a diffuse thickening of the membranes with, as a rule, superficial involvement of the brain substance. The affected membranes are swollen and gelatinous, and patches of necrosis and caseation may be present, the condition being then known as *gummatous meningitis.* As can be readily understood, various cranial nerves, especially the optic and oculo-motor nerves, become implicated, and thus symptoms of irritation or paralysis result. The condition may affect also the roof of the fourth ventricle and give rise to hydrocephalus. On microscopic examination the usual histological changes are found—proliferation of connective tissue cells and thickening of fibres, accompanied by abundant infiltration of lymphocytes and plasma cells (Fig. 467); reactive endarteritis is a common accompaniment. Cellular infiltration occurs round the small vessels penetrating the brain substance and there is neuroglial proliferation in the superficial parts. Syphilitic *pachymeningitis* occurs especially

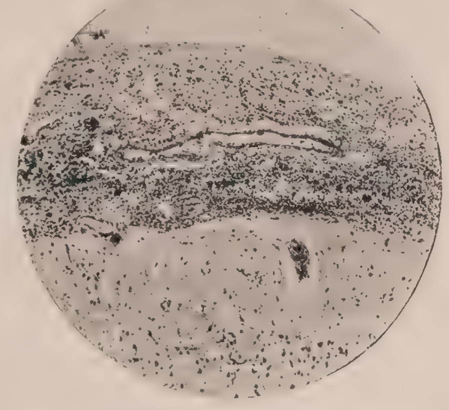

FIG. 467.—Syphilitic Leptomeningitis, showing thickening of Pia-arachnoid with marked cellular Infiltration. × 60.

over the hemispheres and all stages of transition to gumma may be observed.

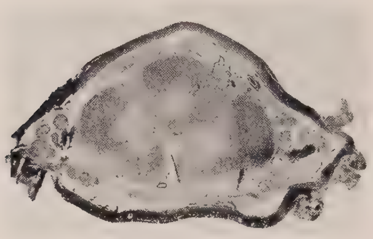

FIG. 468.—Section of Cord in hypertrophic Cervical Meningitis, showing thickening of Dura and adhesion to Arachnoid.

In connection with the *spinal cord*, corresponding lesions are met with. A syphilitic leptomeningitis is of common occurrence and may affect a considerable part of the cord ; it is accompanied by a varying degree of superficial sclerosis. Arterial changes are prominent and softening may follow from interference with the blood supply. Syphilis thus may cause a form of myelitis, as will be described below (p. 766). A comparatively rare condition, which has been known for some time under the name of *hypertrophic cervical pachymeningitis,* has been found to be produced mainly by syphilis (Fig. 468). In this condition the dura becomes markedly thickened, and partly or generally adherent to the arachnoid. The soft membranes also undergo thickening, and a varying amount of sclerosis occurs in the spinal cord. As the name implies, the lesion is commonest in the cervical region and the nerve roots may be pressed on or invaded by the dense connective tissue and undergo a certain amount of atrophy.

Gummata occur in connection with the membranes and are to be regarded simply as an extension and intensification of meningitis. Not infrequently they are multiple. When originating in the soft membranes, they extend inwards and have a somewhat rounded or irregular shape ; the central parts may be diffusely necrotic or multiple foci of necrosis may be present. Gummata growing from the dura are usually flattened and may cover a considerable proportion of a hemisphere (Fig. 469). The soft membranes become adherent, and there may be superficial softening of the brain, probably from in-

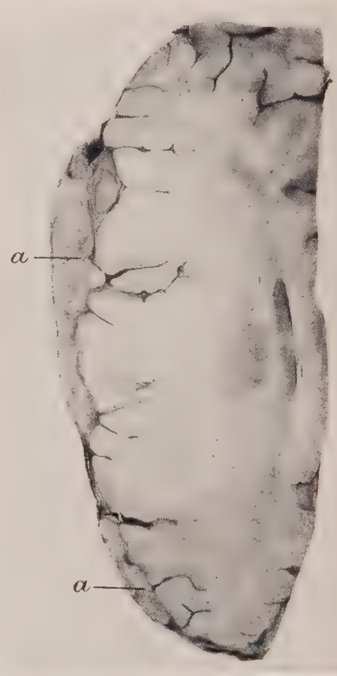

FIG. 469.—Section of Hemisphere above level of Corpus callosum, showing large Gummatous Masses (*a*) growing from the Dura and overlying the surface of the Convolutions.

volvement of the small vessels. A gumma growing from the outer aspect of the dura may affect chiefly the bone, leading to erosion; pressure may be exerted on the brain, or there may be actual growth in an inward direction.

The *arterial changes* are mainly an obliterative endarteritis usually accompanied by cellular infiltration in the perivascular tissue. Great thickening of the intima occurs and sometimes actual obliteration, while thrombosis is a common result. These lesions are of course met with in marked degree in the areas of syphilitic meningitis and in connection with gummata. But they may affect other vessels and occur in parts where there are no other lesions. Small gummata may occur along the lines of the small vessels and the central necrosis may extend to the vessel wall—the so-called *gummatous arteritis*. These various vascular lesions produce their effects by the narrowing or actual occlusion of the affected vessels, thus leading to softening. It is possible that a gummatous patch may weaken the arterial wall and give rise to an aneurysm, but we believe that cerebral hæmorrhage rarely occurs as the result of a syphilitic lesion.

General Paralysis of the Insane. In this disease there occur very widespread lesions in the nervous system, and the resulting symptoms are motor and sensory as well as mental in nature. It is now regarded as a syphilitic condition, and stands in pretty much the same relation to the tertiary stage as does locomotor ataxia. Like the latter it occurs some years after the period at which tertiary manifestations are met with, and it is much commoner in the male than in the female sex. It is occasionally met with as a sequel to congenital syphilis, appearing usually about the age of ten or somewhat later. The *Treponema pallidum* has been found in the brain in a certain number of cases, even apart from the lesions. The organism appears to have an irregular distribution, so that while in some cases it may be found in large numbers, in others its presence cannot be demonstrated. The chief changes are on the one hand degeneration of nerve cells and fibres, especially in the grey matter, and on the other, reactive thickening of the neuroglia and soft membranes. Probably neither of these is to be regarded as produced by the other, but rather both are the effect of the same toxic agency.

STRUCTURAL CHANGES. The following is an account of the changes which may be commonly found in an advanced stage of the disease. The dura mater is usually abnormally adherent and somewhat thickened, and the inner aspect on one side or both sides may be covered by a brownish membranous layer, ordinarily known as pachymeningitis hæmorrhagica. This is simply the result of extravasation of blood under the dura (p. 721). Such extravasation is believed by some writers to occur during the congestive attacks of convulsive nature, which are common in the disease. The arachnoid over the hemispheres shows varying degrees of opacity and thickening, while the sulci are widened and contain an excess of fluid; the tissue along the sulci has a somewhat gelatinous character, but collapses as the fluid runs out. Sometimes the pia-arachnoid cannot be stripped from the surface of the convolutions in the normal way, and small portions of the grey matter are removed along with it, leaving a somewhat worm-eaten appearance on the surface of the convolutions. This condition, if present, is usually most marked over the frontal lobes. The superficial grey matter is somewhat thinned, and the normal marking of parallel laminæ may be imperfect or blurred. The causes of these changes will be readily understood from the histological examination. The ventricles are widened and contain an excess of fluid, this being, along with the widening of the sulci, the result of atrophy of the brain substance. Not infrequently minute excrescences or granulations, composed of local proliferations of neuroglia, are present in the ependyma. The floor of the fourth ventricle is a common site of these.

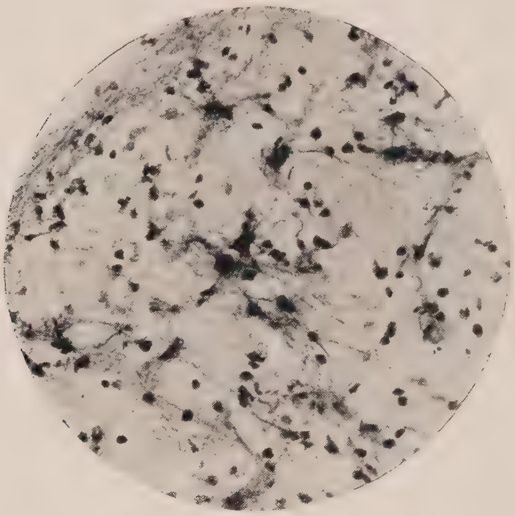

FIG. 470.—Section of Cerebral Cortex in general Paralysis of the Insane showing "Spider Cells" and increase of Glial Fibres. × 250.

On MICROSCOPICAL EXAMINATION, the cortical grey matter is seen to be much more cellular than the normal, owing chiefly to increase of neuroglial cells. The small nutrient vessels stand out more prominently, from their being surrounded by lymphocytes and proliferated cells, and their course is somewhat irregular. There is a general increase of neuroglia fibres, whilst the neuroglia cells are much enlarged and branched, constituting the well-known 'spider-cells.' These cells are specially abundant in the superficial parts where, with the increased fibres, they constitute the sub-pial felting (Fig. 470). They are abundant also round the small vessels, and some are attached by their processes to the vessel wall. The mesoglial cells or 'cerebral histiocytes' also are enlarged and increased in number, and many of them give an iron reaction. The normal arrangement of nerve cells is disturbed, and it has been determined that many disappear; of those surviving, many show various signs of degeneration. There is also considerable degeneration and loss of nerve fibres. These changes, though especially marked in the cortical grey matter, are not confined to it, and sclerotic change may also be present in subjacent white matter and in other parts of the brain. There may be systematic degeneration in the spinal cord, and a degree of lateral sclerosis is not uncommon. In other cases there is sclerosis in the posterior columns, and occasionally the typical lesions of tabes dorsalis are superadded. Corresponding motor and sensory disturbances are then present, and there may also be trophic lesions, including Charcot's disease of joints (p. 770).

The resulting *symptoms* are many and can be explained only in a general way. Disturbances of the mental functions are amongst the earliest and are varied; alteration in disposition and in moral qualities, loss of memory and especially grandiose ideas are amongst the commonest. Ultimately there is dementia. These symptoms are related to the progressive changes in the neurons especially in the frontal lobes, there being interruption of the association fibres, degeneration and ultimately disappearance of the cells. Corresponding changes in the motor neurons lead likewise to a variety of disturbances, first in the finer movements. Tremor of the lips and tongue, interference with articulation, inequality of the pupils, etc., are examples. General weakness of progressive nature is present. Another feature, as has already been mentioned, is the occurrence of convulsive seizures or 'congestive attacks,' with loss of consciousness.

General paralysis is usually a chronic disease, but some cases run a comparatively acute course, and in them, of course, the neuroglial proliferation is less in evidence. It may be noteworthy only under the pia, and degenerative change in the nerve elements is less marked. Often a striking feature is the marked perivascular infiltration with round cells, lymphocytes and plasma cells, these often forming a distinct sheath or mantle to the vessels.

Tabes dorsalis is more conveniently described in connection with diseases of the spinal cord (p. 767).

In general paralysis there is usually a considerable increase in the cell content of the *cerebro-spinal fluid*, the number of cells being not infrequently 50 per c.mm. or more. The cells in excess are chiefly lymphocytes but a small proportion of mononuclears and plasma cells also are present. There is besides a considerable increase of the proteins and the fluid almost invariably gives a positive Wassermann reaction. The Lange gold test usually gives a paretic reaction.

In connection with the pathology of general paralysis, it may be noted that in *sleeping sickness* somewhat similar changes, though of minor degree, are present in the nervous system. These are of proliferative type with lymphocytic infiltration, and occur in the membranes and superficial parts of the brain, in fact a mild meningo-encephalitis is present. In this disease the trypanosomes are present in the cerebro-spinal fluid, and the lesions are evidently the result of diffusion of toxins from the fluid into the superficial parts of the brain.

CHAPTER XVII

THE NERVOUS SYSTEM (*continued*)

THE SPINAL CORD AND THE NERVES

THE SPINAL CORD

Whilst the diseases of the spinal cord are of the same nature as those of the brain, we find great differences as regards the relative frequency of different lesions. Thus, for example, the spontaneous hæmorrhage and softening from embolism, which are so frequent in the brain, are extremely rare in the cord. Tumour growth also is less often met with, and we may say that tumours in the substance of the cord are specially rare, although it is not infrequently involved by growths from the meninges or the bones. On the other hand, certain tracts of fibres and groups of nerve cells are often the site of lesions, and these, which form the basis of the *systematic diseases*, constitute an important group. It is further to be noted that, owing to the relatively small size of the cord, when a gross lesion is present the cord is not infrequently involved in its whole thickness; such a lesion is known as a transverse lesion, and we shall consider the main varieties.

Transverse Lesions. Such lesions may be either slowly or rapidly produced, and may result from pressure from outside or from a primary affection of the cord. A transverse lesion may be the result of injury, a *fracture-dislocation* not infrequently causing destruction of the cord in its whole thickness. Spontaneous *hæmorrhage* may occasionally produce the effects of a transverse lesion, but, as has already been said, such an occurrence is very rare. *Tuberculous disease* of the bodies of the vertebræ is a fairly common cause. It leads to marked angular curvature of the spine and the cord may be injured mechanically; or, in other cases, chronic tuberculosis of the membranes is set up and the spinal cord may undergo secondary softening at the site. The effects of *syphilitic meningitis* thus sometimes extend deeply, and may produce the results of a transverse lesion. The cord is not infrequently pressed upon by *tumours* of the vertebral column (Fig. 471), and a meningioma, growing from the membranes, is occasionally the cause of compression. Also the conducting functions of the spinal cord may be interfered with by an area of *acute myelitis*, the symptoms then developing rapidly, or the interruption may occur more gradually as a result of a patch of chronic myelitis.

The results of a transverse lesion, besides the local damage, are of the nature of ascending and descending degenerations in the respective tracts of the spinal cord. In the case of recent lesions, the degenerations are best demonstrated by Marchi's method or one of its modifications, and they begin to be distinct about a week after the lesion. The degenerated fibres appear black (Fig. 472), owing to the fact that their myelin has not been completely oxidised by the bichromate solution, and is thus still able to reduce perosmic acid. The method is applicable until the degenerated myelin has disappeared—that is, for several months. In the case of long-standing lesions of the spinal cord, Weigert's method or its modifications may be employed. In this group of methods the normal myelin is stained darkly, and accordingly, when the degenerated myelin has become absorbed, the affected tract appears as a pale area.

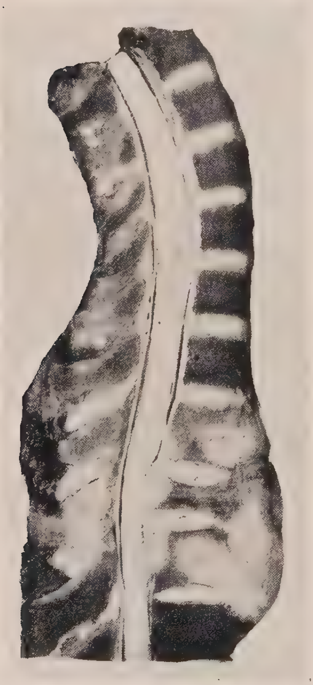

Fig. 471.—Vertical mesial section of the Vertebral Column in cervical region, showing multiple Nodules of Sarcoma pressing on the Cord.

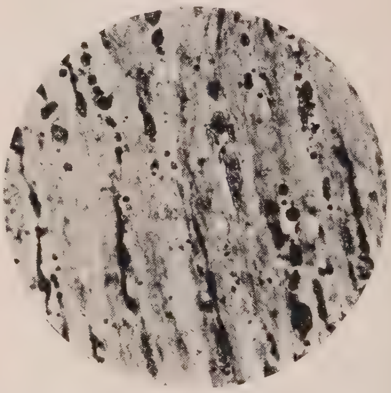

Fig. 472.—Longitudinal section of posterior Columns of Spinal Cord in process of degeneration.

The degenerated material stained black by Marchi's method. × 170.

When there is compression of the spinal cord by a gross lesion so as to cut off the subarachnoid space below, the cerebro-spinal fluid in the latter comes to acquire definite features. There occurs a great increase of protein and the fluid shows massive coagulation on being removed from the body ; it has also often a yellowish colour (xanthochromia). The cells may or may not be increased; if increase is present it is on the part of the mononuclears. These changes are grouped under the term 'Nonne-Froin syndrome.'

Ascending Degenerations. If we take as an example a comparatively recent lesion at the level of the lower dorsal region, we find the following ascending degenerations in a section stained by Marchi's method, from a part shortly above the lesion (Fig. 473, *A*). In the posterior columns, Burdach's and Goll's columns show degeneration, with the exception of an area behind the posterior commissure where there are chiefly commissural fibres. At a higher level, however, the degenerated area on each side recedes from the posterior cornu, and in the cervical region the degeneration is practically confined to the internal half of the posterior columns. Thus the fibres in the posterior columns are arranged according to the level from which they come, the innermost fibres coming from the lowest roots. And we may say in a general way that in the cervical region Goll's column is mainly constituted by fibres from the lower extremities, Burdach's by fibres from the upper. (Degenerations in Burdach's and Goll's columns extend up to their respective nuclei in the medulla, namely, the nucleus cuneatus and nucleus gracilis; in these nuclei there is a new set of neurons, whose axons pass upwards chiefly in the median fillet, in which they decussate—upper sensory decussation—to the lower part of the optic thalami.) In the lateral columns there is degeneration in the direct cerebellar tract, which arises from Clarke's vesicular column and extends up to the restiform nucleus in the cerebellum. As Clarke's column does not extend below the first lumbar segment, the cerebellar tract will not be degenerated when the lesion is below that level. In front of this tract, there is a fairly large superficial area of degeneration corresponding to

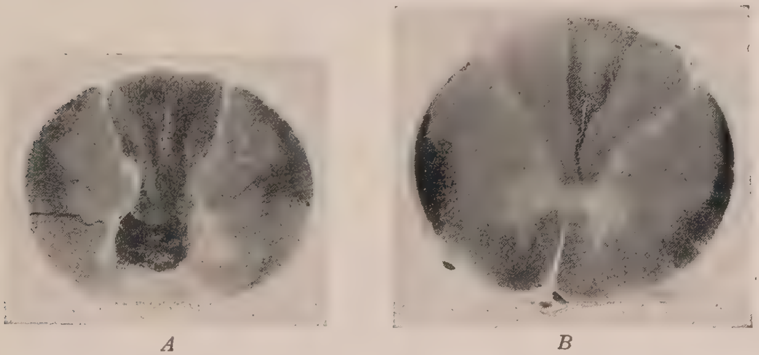

FIG. 473.—Sections of Spinal Cord above transverse lesion in lower dorsal region; the degenerated fibres appear black.
(*A*) Immediately above the lesion (the rounded degenerated area in front is part of the local softening).
(*B*) In cervical region. (Marchi's method.)

the antero-lateral ascending tract of Gowers; and in front of this again there is usually a thin layer of degenerated fibres on the surface of the cord round to the anterior fissure (Fig. 473, *B*). Most of the degenerated fibres of the antero-lateral tract can be traced up to the middle lobe of the cerebellum.

In connection with lesions of the sensory fibres in the cord, it is important to bear in mind the disposition of the fibres entering the cord at the posterior nerve roots. They divide into two main portions, the one set becoming at once part of the postero-external tract, and when the posterior root is injured or destroyed, these fibres degenerate up to the nuclei in the medulla. At a level above the lesion, these ascending fibres are constantly being displaced towards the middle line by the incoming fibres, as has been explained. The other fibres of the posterior roots pass (*a*) to cells in the anterior cornua, completing the reflex arc, (*b*) to cells in Clarke's column, and (*c*) to cells in the posterior cornua. From these last, ascending sensory fibres take origin and soon pass across the middle line to the lateral columns, where they ascend in the antero-lateral tract. Degeneration accordingly does not occur in this tract when the posterior roots are cut, or when, as in locomotor-ataxia, they are destroyed by disease. On the other hand, these decussating fibres are frequently interrupted by the lesion round the central canal in syringomyelia (p. 783), and in this case sensation to heat and to pain is interfered with.

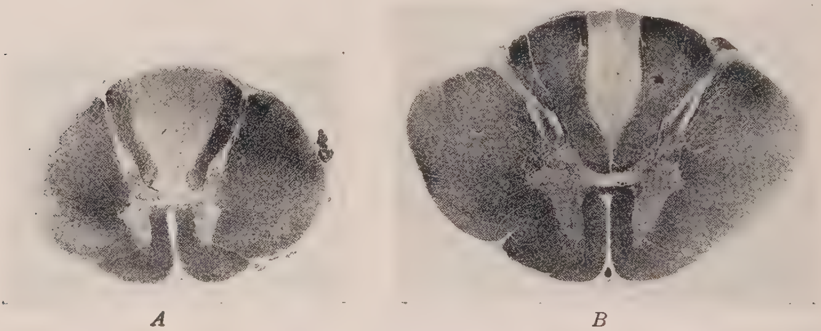

FIG. 474.[1]—Ascending Degeneration resulting from destruction of Cord by cancerous growth at tenth dorsal segment.
(*A*) A short distance above the lesion.
(*B*) In cervical region; the degeneration is confined to Goll's column.
(Weigert-Pal method.)

Descending Degenerations. These are met with in two chief conditions, namely (*a*) when there is an interrupting lesion in the cord, and (*b*) when the lesion is at a higher level. The commonest example of the latter is destruction of the motor fibres in the internal capsule or destruction of the motor cells of the cortex, softening being the most frequent lesion. Complete destruction of the motor fibres, with hemiplegia, is generally caused by a capsular lesion, and in such a

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[1] Figs. 474, 478, and 481 are from preparations by the late Dr. Alexander Bruce, kindly lent to me by Dr. A. Ninian Bruce.

case there is degeneration of the crossed pyramidal tract on the opposite side and of the direct pyramidal tract on the same side (Fig. 475). In addition, there may be seen by Marchi's method some scattered degenerated fibres in the crossed pyramidal tract on the same side as the lesion, that is in some motor fibres which have not crossed in the medulla. As the direct pyramidal tract does not usually extend lower than the first dorsal segment, degeneration in it will not appear in sections below that level. It contains only a small proportion of the fibres, less than a tenth, and in a certain proportion of cases is absent altogether. In the case of a *transverse lesion* of the cord the most marked degeneration is in the crossed pyramidal tracts, and, as such a lesion is commonest in the lower part of the cord, the direct pyramidal tracts are usually not involved. There may be seen by Marchi's method scattered degenerated fibres in the superficial parts in the lateral column in front of the crossed pyramidal tract, and also in the anterior column round to the median fissure. These belong to Monakow's bundle, which comes from the red nucleus, and to minor bundles from medulla, corpora quadrigemina, and thalamus. It is to be noted that in sections stained by Weigert's method, such degenerations are not recognisable, owing to the scattered arrangement of the fibres.

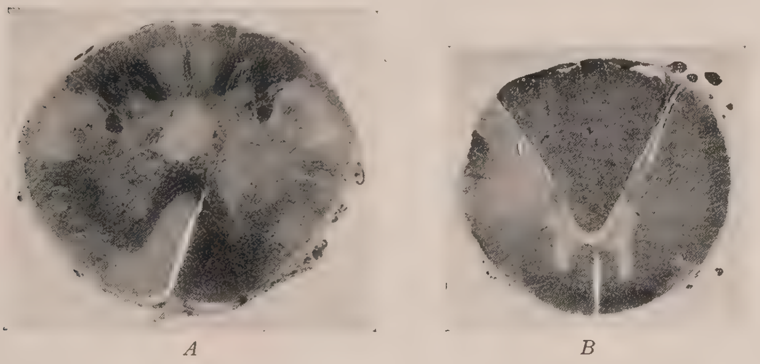


Fig. 475.—Lesions in Hemiplegia.

(*A*) Transverse section of medulla. The anterior pyramid on one side is degenerated and appears pale.

(*B*) Section of spinal cord in dorsal region, showing the degenerated crossed pyramidal tract on one side (from another case with lesion on opposite side to that in *A*). (Weigert-Pal method.)

INFLAMMATORY CHANGES

Acute Myelitis. Acute inflammation of the substance of the spinal cord attended with softening, is commoner than the corresponding affection of the brain (suppurative lesions being excepted), but our knowledge of its etiology is very unsatisfactory. The cord may be injured by fracture-dislocation or as a result of disease of bone, as in tubercle, a ‘compression myelitis’ then being produced; also inflammatory or suppurative affections of the meninges may involve the cord and cause myelitis of its superficial parts to a varying degree. Apart from such conditions, however, the nature of which presents no difficulty, there is a fairly large group of cases of obscure nature. Myelitis has been found not infrequently to follow exposure, especially of the lower extremities, to cold and wet, and such conditions may possibly affect the circulation of the cord directly or make it more susceptible to toxic influences or infections.

Myelitis occurs also in *bacterial infections*, fevers, such as typhoid, puerperal conditions, etc.; and it has sometimes been found to be associated with gonorrhœal infections. In such cases the myelitis is set up by means of the blood stream, but to what extent toxic action or secondary invasion by organisms is responsible is not clear; though in certain cases the presence of typhoid bacilli, pneumococci, streptococci, etc., has been detected. The occurrence of small abscesses in the spinal cord—*suppurative myelitis*—is very rare. They are sometimes met with in such conditions as pyæmia, bacterial endocarditis, septic cystitis, etc.; the suppuration tends to spread in the long axis of the cord. It is believed by some, moreover, that organisms may reach the cord by spreading along the sheaths of the spinal nerves in conditions such as cystitis, bed sores, dysentery, etc.

Myelitis of various types is often due to *viruses*. It is usually of the disseminated type and is associated with similar lesions in the brain—that is, is part of an encephalomyelitis. Not infrequently, however, lesions are more marked in the spinal cord and paraplegia may sometimes result. Such an infection has been met with after vaccination and various fevers, such as smallpox and measles, but it also occurs independently of any previous condition. Details with regard to these are given in connection with encephalitis (p. 739). Further, it has now been shown that anterior poliomyelitis (p. 773) is really the result of a general virus infection of the nervous system, the chief effects of which are on the nerve cells.

In recent years the important part played by *syphilis* in connection with myelitis has come to be recognised, and, according to Buzzard and Greenfield, 80 per cent. of cases are due to this disease. Syphilitic myelitis may occur at a comparatively early stage, sometimes within two years after infection, though, as a rule, it appears later; and the affection of the cord is generally secondary to syphilitic leptomeningitis, which is usually more extensive than the myelitis. The resulting softening is chiefly the result of changes in the small arterioles. Syphilitic myelitis is most frequent in the dorsal region.

Structural Changes. The appearances of the cord in acute myelitis vary much both in severity and in distribution. Sometimes the disease is confined to one or two segments—*transverse myelitis*;

sometimes a considerable part of the cord is affected—*diffuse myelitis*; and, again, there may be multiple distinct foci, sometimes quite small—*disseminated myelitis*. The affected parts may have a soft consistence, and the markings, notably the distinction between the white and grey matter, are blurred; in extreme cases the substance is quite pulpy and all structure has disappeared. In other cases there may be merely areas of congestion, sometimes attended by small hæmorrhages. Often, however, especially in the disseminated type, the lesions are recognisable only on microscopic examination. They vary greatly in different cases and further details will be found in connection with encephalitis (p. 739). The later stages are characterised by secondary Wallerian degeneration, according to the nerve tracts destroyed by the inflammatory softening and by overgrowth of the neuroglia.

Chronic Myelitis. This need hardly be described separately as so many conditions are included under the term. Characterised especially by overgrowth of neuroglia, it may follow acute myelitis, or it may be produced by similar causes acting less intensely; it is common also in the superficial parts of the cord as the result of chronic meningitis. The overgrowth of neuroglia secondary to systematic degenerations and also that following destruction of the nervous structures as a result of vascular disease, should be called 'secondary sclerosis' and not myelitis, though the latter term is sometimes used.

Spinal Meningitis is described above along with cerebral meningitis (p. 736).

LESIONS OF THE SENSORY NEURONS

Tabes Dorsalis or Locomotor Ataxia. This disease is an affection of the lower sensory neurons and is characterised chiefly by degeneration of the posterior root fibres and their upward prolongations in the spinal cord; though there are changes in other parts of the nervous system also. From clinical observations alone, the view came to be held by many that tabes was a late result of syphilis—a *parasyphilitic* affection, as it was called; and the use of the Wassermann test has confirmed the view as to its syphilitic origin, a positive reaction being given by both blood and cerebrospinal fluid in the majority of cases. It has been noted that when the symptoms of tabes appear, a previously negative Wassermann reaction may change into a positive one, and as such a phenomenon is generally associated with renewed activity of the syphilitic virus, tabes may be regarded as of true syphilitic nature rather than as a sequela. The *Treponema pallidum* has been found in the cord in only a few instances. It is now generally admitted that there is no definite evidence that tabes ever occurs apart from syphilitic infection. It is to be noted that as regards their relation to syphilis and period of occurrence, there is a similarity between tabes and general paralysis, and occasionally the two affections are present together, though one is usually more marked than the other.

Tabes is much commoner in men than in women (in a proportion of about 9 : 1), and usually a period of about ten years intervenes between the primary syphilitic infection and the appearance of symptoms, though both shorter and longer intervals are met with. In a small proportion of cases it has developed as a result of congenital syphilis, the symptoms then commencing at a proportionately early period of life. In the great majority of cases the disease, as indicated by the lesions in the posterior roots, starts in and affects the lower portion of the cord—the lumbar enlargement—and gradually fades off in an upward direction, so that the upper dorsal roots may be practically healthy. In a small proportion of cases, however, tabes affects chiefly the region of the cervical enlargement, where the posterior roots show the characteristic changes; such cases constitute the *cervical type* of tabes.

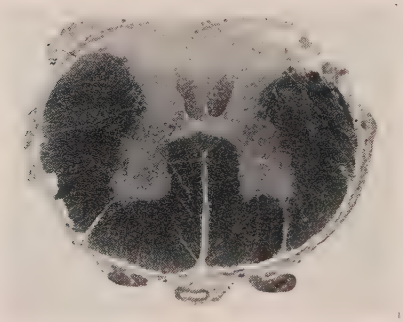


Fig. 476.—Section through Lumbar Enlargement of Cord in a case of Tabes dorsalis, showing the Degeneration in the posterior Roots and posterior Columns. (Weigert-Pal method.)

Structural Changes. If the spinal cord from a marked case of the common type be examined, it can usually be seen that the posterior columns in the lumbo-sacral region are somewhat shrunken, and have a greyish colour; the pia-arachnoid over them is thickened. The posterior roots appear wasted and many have a distinctly grey tint contrasting with the white colour of the anterior roots, these changes, as already explained, gradually fading off in an upward direction. In sections through the lumbar enlargement, stained by the Weigert-Pal method, the following are the chief changes observed where the disease is well marked. In the posterior roots proximal to the ganglia, there is seen to be a considerable degeneration and loss of the fibres, as indicated by the pale staining, and this degeneration becomes more marked still in the root fibres inside the cord. The posterior cornua also have lost medullated fibres to a considerable degree and thus appear pale (Fig. 476). The posterior columns show marked degeneration and sclerosis, though there are usually a considerable number of non-degenerated fibres just behind the posterior commissure; these represent endogenous or commissural fibres which are not affected. At higher levels it is found that the root fibres gradually become less affected, until ultimately they appear healthy. When this level has been reached, it is seen that the degenerated fibres of the posterior columns have become separated from the posterior cornua by a layer of healthy fibres, which represent the root fibres which have entered the cord above the level of the actual disease. Thus, for example, in the cervical region the changes represent merely an ascending degeneration as the result of the disease at a lower level. In the *cervical form* of tabes the posterior roots show degeneration similar to that described, and the outer parts of the posterior columns are chiefly involved. The degeneration in tabes does not extend higher than the nucleus gracilis and the nucleus cuneatus, that is, the upper terminations of the long fibres of the posterior columns.

The affected parts of the cord show the usual changes secondary to degeneration of the nerve fibres. The neuroglia becomes thickened, as do also the walls of the small vessels, and corpora amylacea are often present in the sclerosed tissue. In advanced cases the thickened neuroglia may involve and lead to secondary atrophy of other nerve fibres. In the posterior root ganglia degenerative changes may be found in the nerve cells—chromatolysis, atrophy and disappearance of the cells, and interstitial overgrowth. But such changes may be hardly appreciable and appear always to be of less degree than those in the ascending axons. The thickened pia-arachnoid over the affected part of the cord is to be regarded merely as a secondary change. There is no evidence that, as some have supposed, it represents a primary meningitis which leads to constriction of the ingoing fibres and to degeneration beyond. Degenerative changes have been found also in the peripheral nerves corresponding to the affected roots, these changes being chiefly in the small terminal twigs.

Changes occur also in the sensory neurons in the higher parts of the central nervous system. Atrophy of the optic discs and optic nerves is common, as is also the Argyll-Robertson phenomenon, in which there is a loss of the light reflex while movement of the pupils in accommodation is retained. Degenerative changes may be present also in the sensory cranial nerves and in their nuclei—the trigeminal, auditory, glosso-pharyngeal and vagus. They have been described, besides, in connection with the sympathetic system, and have been taken as explaining the severe attacks of pain and sickness—the ‘gastric crises’—which are sometimes a marked feature of the disease, though the lesions of the vagi also may be concerned in their production.

Such widespread lesions as have been described are necessarily attended by marked disturbance of sensory function. The afferent fibres first affected are chiefly those from the deeper structures, the muscular sense being early impaired, and loss of co-ordination and ataxia resulting. The sensation of pain, especially in the deeper structures, is affected before tactile sensation, though the latter also becomes impaired and paræsthesia is a common condition. Severe shooting pains in the limbs—‘ lightning pains ’—also occur, and there is often a ‘girdle sensation,’ or feeling of constriction, round the trunk at a level corresponding with the upper limit of the disease. The lesions in the posterior root fibres described above necessarily lead to an interruption of the reflex arc and accordingly the tendon reflexes disappear ; absence of the knee-jerk is thus a well-recognised phenomenon.

The cerebro-spinal fluid shows changes of fairly constant character. The cells are increased in number, often numbering 50 per c.mm. or more ; they are chiefly lymphocytes but large mononuclears and occasionally even a few polymorpho-nuclears may be found. The protein is normal or slightly raised and there is usually a globulin reaction though it may be weak. The Lange colloidal gold test as a rule gives a luetic reaction.

OTHER EFFECTS. In addition to interference with the sensory functions and irritation of the sensory nerves, various trophic disturbances are of common occurrence. Thus in the skin, herpes and pemphigoid eruptions are met with, and an interesting and fairly common lesion is perforating ulcer which starts in the sole of the foot, passing deeply into the tissues, and is of very intractable nature. Of great interest are the trophic lesions which occur in the joints and bones. The former are not infrequently the seat of what is known as ‘ Charcot’s disease,’ as the changes were first fully described by him. The hip-joint and the knee-joint are those most commonly affected, though the ankle-joint also may be the seat of the disease ; more rarely the joints of the upper extremities. There occurs first of all a painless effusion into the joint, which may lead to great stretching of the capsule. The fluid is at first clear but later may contain flakes of inspissated lymph. The cartilage becomes eroded, and there is irregular absorption with new formation of bone, so that the configuration of the head of the bone becomes much altered (Fig. 477). Along with these changes, softening and stretching of the capsule of the joint occur, and spontaneous dislocation is not uncommon. In the long bones considerable atrophy and rarefaction may be present, and sometimes spontaneous fracture follows.

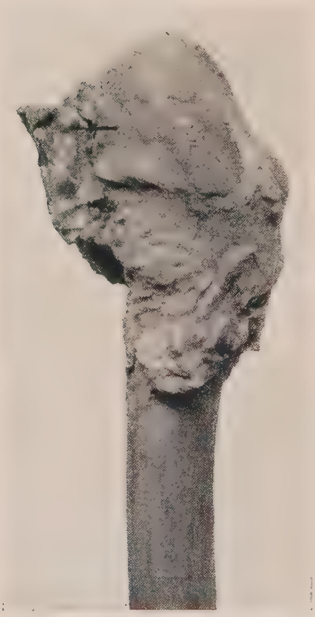


FIG. 477.—Upper end of Femur in Charcot’s disease of Hip-joint in a case of Tabes.

Note the irregular absorption of the head and the new formation of bone below.

We see that tabes may be regarded as an affection of various sensory neurons, especially those of the posterior root ganglia of the lower part of the cord, and that the degenerative effects appear more marked in the long axons related to them than in the cells themselves. Moreover, the affection is probably to be interpreted as the result of the diffuse action of syphilitic toxin rather than of the local presence of the spirochætes. Tabes occurs in only a small proportion of cases of long-standing syphilis, and some authorities consider that excess of functional activity of different parts of the nervous system, in addition to the presence of syphilis, has an important effect in determining the site of the lesions. But regarding this nothing definite can be affirmed.

Friedreich's Ataxia. This disease, in which there is sclerosis in both motor and sensory tracts, often affects more than one member of a family, hence sometimes called *family ataxia*; it rarely occurs in successive generations. Isolated cases of the disease also are met with. It usually begins in the years before adolescence and the chief symptoms are ataxia with muscular weakness. Lateral curvature of the spine and talipes equinus are often present, and nystagmus and affections of speech also are common. In such cases, the spinal cord has been found to be relatively thin and sclerosis has been present in the posterior and lateral columns (Fig. 478). The posterior roots show degeneration, especially the fibres within the cord, and the affection of the roots and posterior columns may be present in the cervical region as well as lower down; the cells in the posterior root ganglia, however, are little altered. In the lateral columns the pyramidal fibres are degenerated, the degeneration being most marked, below, and diminishing in an upward direction. The direct cerebellar tracts are similarly affected, and the cells of Clarke's vesicular column show degenerative changes. There may be some degeneration also in the ascending antero-lateral tracts. The nature of the disease is obscure and there seems to be no relation to syphilis. The view has been put forward that the disease represents a condition of incomplete development, whereby certain systems of fibres are in a sense shorter-lived than usual and undergo degeneration, which appears first in the distal parts of the long axons.

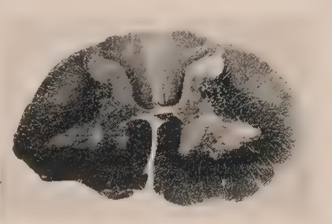


Fig. 478.—Section of Cord in Friedreich's ataxia, showing Degeneration in posterior and lateral Columns.
(Weigert-Pal method.)

Herpes Zoster. In its ordinary form this disease may be said to be the result of an acute inflammatory lesion of the posterior root ganglia, especially those in relation to the nerves supplying the trunk; a similar affection of the Gasserian ganglion also is sometimes met with. Along the course of the nerves related to the affected ganglia, pain and hyperalgesia occur and are followed by erythema and the formation of vesicles, which contain a serous fluid, sometimes with admixture of blood. In its mode of onset and course, its association with pyrexia, and its incidence sometimes in epidemics, herpes zoster presents the usual features of an acute specific fever; immunity is apparently developed, as a second attack is of very unusual occurrence. The disease presents various points of similarity to acute anterior poliomyelitis, and is likewise due to a filter-passing virus. Inoculation of the rabbit's cornea with vesicle fluid may result in a keratitis, though this occurs less readily than in the case of herpes febrilis (*vide infra*). It has been shown by immunity experiments that the viruses of the two affections are distinct.

The first detailed account of the nervous lesions was given by Campbell and Head, and the chief changes which were met with by these observers are the following. The lesion of the posterior root ganglia is an acute inflammation, attended by infiltration of small round-cells which may form dense aggregations, and by hæmorrhages, while the nerve cells are injured in varying degree; inflammatory change is present also in the capsule of an affected ganglion (Fig. 479). The lesion is sometimes mainly in one focus, usually towards the dorsal aspect of the ganglion, and occasionally its substance may be largely destroyed; sometimes there are multiple small foci. Many of the nerve cells involved in the lesions undergo necrosis and are afterwards destroyed, whilst in other parts they are practically unaffected. As a result of the damage to the nerve cells, secondary degenerations shown by Marchi's method can be traced along the nerve fibres to their peripheral distribution, and also backwards through the posterior nerve roots and for a distance upwards in the posterior columns of the cord. At a later period secondary fibrosis occurs in the various structures which have been damaged. A herpetic eruption of similar distribution is sometimes met with also in chronic disease of the spinal cord, for example, tabes dorsalis or myelitis. It may be produced also by the spread of inflammatory change to a ganglion from a lesion in the neighbourhood, e.g. caries of a rib, and has been found to follow cancerous invasion of a ganglion.

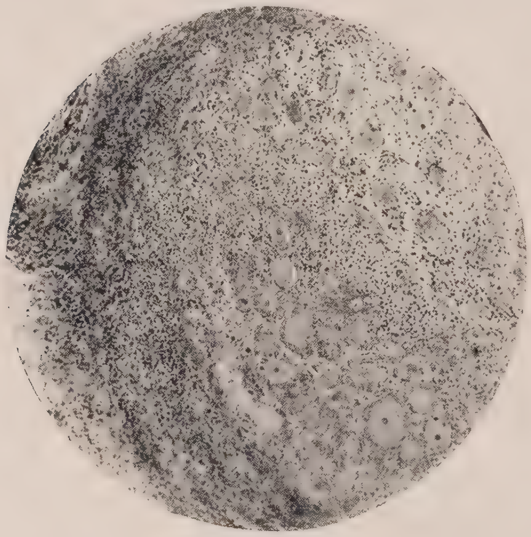


FIG. 479.—Section of Posterior Root Ganglion in Herpes Zoster, showing inflammatory infiltration and destruction of nerve cells. × 80.

Herpes febrilis or labialis. The virus in this condition does not appear to affect the nervous system in the human subject but it readily does so in some of the lower animals. The human infection is characterised by the presence of vesicles on the skin of the face, especially round the mouth. It may occur as a primary condition but it is often secondary to other infections, notably pneumonia and cerebro-spinal fever. This latter fact suggests that the virus may occur in the normal secretions of the mouth, and also raises the possibility that this may be a source of fallacy in the investigation of other virus diseases. Inoculation by scarification of the rabbit's cornea with the vesicle fluid results in a keratitis, and in a certain proportion of cases the virus may spread along the nerves to the brain and cause an encephalitis, in which damage to nerve cells, leucocytic infiltrations, etc., are prominent features; the changes on the whole resemble those in epidemic encephalitis in the human subject. It has recently been shown that the virus travels widely along the nerve fibres throughout the nervous system, this result corresponding with what has been established in the case of the poliomyelitis virus. Both in the epithelium of the lesions and in the affected nerve cells minute granules stainable by Giemsa's method are present and may represent a virus in some form. There are also intra-nuclear eosinophile inclusions in the epithelium, often known as 'Lipschütz bodies.'

LESIONS OF THE MOTOR NEURONS

If the neuro-muscular system as a whole be considered, it is seen that it consists of upper and lower motor neurons and the muscles. Lesions which affect muscular action may be in any one of these, and, further, may be primarily either in the axons or in the nerve cells themselves; there are thus, to speak generally, five possible sites of disease affecting the motor function. What is apparently a primary affection of the muscles is seen in the group of idiopathic muscular dystrophies, while primary affections of the axons of the lower neurons are seen in peripheral neuritis, in the latter case along with sensory involvement; these will be described later. We have here to consider the affections within the spinal cord, and the distinction between the lower and upper neurons is of fundamental importance. Lesions of the former are characterised by paralysis attended by wasting and flaccidity of muscles. On the other hand, in lesions of the upper neurons or of their axons, the pyramidal fibres, paralysis is accompanied by heightened irritability of the corresponding lower neurons—increase of the deep reflexes and tendency to spasm, but without true neuropathic atrophy. Again, the lesions may be distinguished as either acute or chronic in character. There are two main acute motor affections, namely, *acute anterior poliomyelitis* and *Landry's paralysis.* A group of chronic degenerative affections occur in connection with the upper and lower neurons, and different names have been applied according to the main symptoms, namely, *progressive muscular atrophy*, *amyotrophic lateral sclerosis*, *spastic paraplegia.* These are conveniently described together.

Acute Anterior Poliomyelitis or Infantile Paralysis. The lesion in this disease may be said to be an acute inflammatory condition affecting chiefly, though not exclusively, the anterior cornua, and leading to destruction of the motor neurons, with corresponding paralysis and atrophy of the related muscles. For a considerable time it has been known to occur sometimes in epidemics, and during the great outbreaks of the disease in Europe and America in 1907, it was conclusively proved to be an infective condition produced by a filterable virus. The disease can be produced in monkeys by intracerebral inoculation with emulsion of an affected cord, etc.; and by this method it has been shown that the virus is present in the nasal mucus of a person suffering from the disease and also in the tonsils and lymphatic glands. The infection may be set up in monkeys by inoculation of the scarified nasal mucous membrane; the virus apparently passes by the olfactory nerves to the brain, and it seems likely that this represents the chief mode of infection of the human subject. There is also evidence, however, that the virus may enter by the alimentary canal. It apparently has a wide distribution.

Structural Changes. The disease affects especially the lumbar and cervical enlargements, and these in an asymmetrical manner. On naked-eye examination of the cord in an acute case, there is little to be observed beyond irregular congestion of the membranes over the affected part of the cord, and a similar condition of the anterior cornua which may be attended by some softening and hæmorrhage. On microscopic examination there is found to be a pretty extensive inflammatory condition of the leptomeninges, with infiltration of lymphocytes, plasma cells, and some polymorpho-nuclear leucocytes, but with no fibrinous exudate, as a rule. The condition is present along the nutrient vessels, especially the anterior arteries and their branches, leucocytes being abundant in their sheaths.

In the anterior cornua, where the lesion is always most marked, there is much congestion along with the cellular infiltration; some of the minute vessels may be thrombosed and small capillary hæmorrhages are not uncommon (Fig. 480). The vascular disturbances are sometimes specially prominent. The nerve cells are affected in varying degree. Certain of them undergo degeneration and necrosis, lose their structure and disappear, some becoming the prey of phagocytes; myelin sheaths and axis cylinders become disintegrated in a similar way. Other nerve cells show varying degrees of chromatolysis, though it is remarkable how little altered some of them are, even when surrounded by inflammatory change. There may be little change in the adjacent white matter beyond leucocytic infiltration. The infection tends rather to spread upwards and downwards in the grey matter, so that this may be seriously involved through several segments. In very intense cases, necrotic change rather than leucocytic infiltration may be the main feature and may affect patches of the grey matter. Although the damage done is mainly in the anterior cornua, minor lesions occur in the grey matter in other parts. Occasionally the virus affects the motor nuclei in the medulla and at higher levels, and leads to lesions similar to those in the anterior cornua. There may then result the symptoms of acute bulbar paralysis.

Pathology of the Disease. It was formerly believed that the virus was disseminated by the cerebro-spinal fluid and then invaded the grey matter from the meninges. Recent work shows, however, that the chief mode of spread is along the nerve fibres.

Important results have been obtained by experimental methods with regard to the spread of the poliomyelitis virus in monkeys. It has been shown that when the virus is inoculated into a cerebral hemisphere it spreads downwards throughout the cord, the path being by the axis cylinders (Fairbrother and Hurst). The virus has a special affinity for the neurons of the enlargements; it there first damages the nerve cells, leading to death of many of them, and then the vascular changes, leucocyte emigration and meningeal inflammation occur. The virus is specially abundant where lesions have taken place. Hurst also found that when the virus is injected into the sciatic nerve, lesions first appear in the lumbar enlargement on the same side; the virus then spreads upwards to the corresponding centre in the hemisphere on the other side. It is detected there before it appears in the cervical enlargement. It may be added that it may be present in certain parts, notably the cerebral hemispheres, when there are practically no lesions.

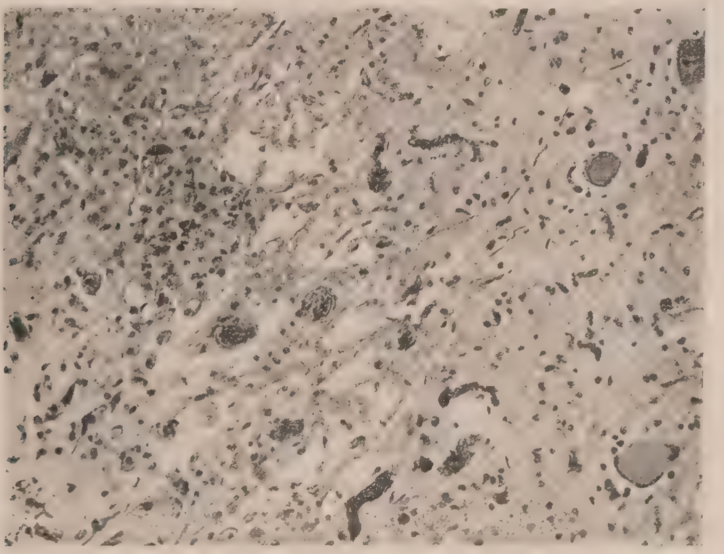


Fig. 480.—Section of Anterior Cornua in Acute Poliomyelitis.

On left side congestion of capillaries, leucocytic infiltration and some softening are present; on the right side degenerating nerve cells. × 150.

Effects. The more acute changes usually pass off in a few days, and many of the motor neurons which are only partially damaged recover; accordingly, considerable diminution in the amount of the paralysis may occur at a later stage. The destructive lesions in the cord are followed by an absorption of the degenerated material and by a proliferation of the neuroglia cells, with subsequent gliosis. Gradually the affected parts shrink, and if the lesion has been a severe one, a distinct difference between the two anterior cornua may be distinguished, even with the naked eye; the anterior nerve roots also become wasted.

In view of the lesions above described, the effects in the peripheral nerves, muscles, etc., can be readily understood. There is a rapid onset of paralysis in the related muscles, though this, as already explained, may in part pass off. Wallerian degeneration occurs in the axons of the destroyed neurons. The permanently affected muscle fibres soon give the reactions of degeneration and undergo rapid wasting, the usual atrophic and interstitial changes occurring in them. Owing to the unopposed action of the unaffected muscles, deformities of the limbs, including various forms of club-foot, etc., are brought about. The bones in the affected limbs may show atrophy, being reduced both in thickness and in density (Fig. 84).

In the cerebro-spinal fluid there is usually at first a marked increase of cells, the numbers sometimes exceeding 500 per c.mm.; as a rule the majority are polymorpho-nuclears and the percentage of these may be very high. Later, there is a gradual fall in the number of cells, the polymorpho-nuclears usually disappearing after a time so that lymphocytes predominate. The protein at first is little changed, but afterwards there is a considerable increase and there may be the formation of a fine fibrin web. The cellular reaction is thus different from that seen in encephalitis lethargica.

Landry's Paralysis. According to the original description this affection is an acute ascending motor paralysis without gross lesion in the nerves or spinal cord. It is commonest in young adult males and comes on suddenly without definite relation to any pre-existing condition. The motor paralysis appears first in the lower limbs and extends upwards, death usually resulting from implication of the higher nuclei. Sensory disturbance is absent or only slight. Cases of this nature are comparatively rare, and in those examined by modern methods, little has been found beyond congestion of spinal grey matter and a certain amount of chromatolysis of the motor neurons, especially in the lower part of the cord—no destructive lesion has been present. This result would point to the action of a toxin leading to paralysis of the nerve cells—an effect, one might say, of a nature opposite to that produced by tetanus toxin. The general characters of the disease, and the fact that enlargement of the spleen and lymphatic glands has been observed in some cases, indicate that the disease may be of the nature of an infection. Bacteriological investigation has given divergent results, and at present nothing definite is known as to the causal agent. It is not possible to say whether the effects on the cord are due to toxic action or to actual invasion of the cord by an organism, possibly of the nature of a filterable virus.

Chronic Disease of the Motor Neurons. The motor neurons may be affected by systematic degenerations, insidious in origin and slow in progress. Both lower and upper neurons are affected together in the great majority of cases, and then there is a combination of atrophic and spastic conditions, the term *amyotrophic lateral sclerosis* being applied. In a comparatively small group the changes are chiefly atrophic, and the main lesions are in the motor cells of the anterior cornua, though not confined to them; the condition known as *progressive muscular atrophy* then results. Though cases are met with clinically where spastic paralysis without atrophic change is present, it has been questioned whether there is a pure *lateral sclerosis* due to affection of the upper neurons alone. It would seem that all these conditions should be regarded as constituting one affection, which varies in its symptomatology according to the proportion in which the different neurons and their axons are involved. With regard to the varieties of such affection, the general statement may be made that nothing definite is known regarding their etiology. They occur in middle and late adult life, much more frequently in men than in women, and while various conditions have been put forward as causal factors, none of these are regularly related to the origin of the affection. There is also no evidence that syphilis is a main cause of these degenerations of the motor neurons; but a syphilitic myelitis may lead to a degeneration in the pyramidal tracts, which clinically may resemble a primary lateral sclerosis. We shall now give some facts with regard to these affections.

Progressive Muscular Atrophy. In cases where atrophic changes are the outstanding feature, the lesion, as has been stated, is mainly a progressive degeneration of the neurons in the anterior cornua. It usually starts in the cervical enlargement in the neurons related to the small muscles of the hand. The affected muscles are the seat of fibrillar twitchings, and gradually atrophy with corresponding weakness follows. But owing to the slow progress, the actual change in the muscles at any one time is not sufficient to give rise to the reaction of degeneration. The thenar and hypothenar eminences become markedly wasted, the interossei also become affected, and the hand assumes a characteristic claw-like form. The affection then extends to the muscles of the arm and those of the shoulder girdle; as already mentioned, the symptoms of bulbar paralysis may appear as a terminal phenomenon. In one type of the disease the wasting appears first in the muscles of the shoulder girdle. In the anterior cornua corresponding to the wasting, the process is a progressive atrophy of the neurons. It is seen that some of them have disappeared, while many of those remaining show stages of atrophy; many have lost their processes and become irregular, or are somewhat oval in form; pigmentary changes are sometimes prominent. There is a certain amount of neuroglial overgrowth, but as a rule it is not a marked feature. The anterior spinal roots become wasted and may appear somewhat grey and thinner to the naked eye, whilst in the related muscles the atrophy corresponds to the affection of the neurons and is irregular in distribution.

Amyotrophic Lateral Sclerosis. In the cases classified as progressive muscular atrophy, there is to be seen in sections of the cord stained by Weigert's method, a certain amount of disappearance of medullated fibres in the anterior cornua and in the ground bundles outside, and it may be in the crossed pyramidal tracts ; this indicates a certain involvement of the axons of the upper neurons. In cases, however, where a spastic condition occurs early and is a prominent feature, there is a much more extensive involvement of the upper neurons. In addition to the atrophic changes in the anterior cornua, the crossed and usually also the direct pyramidal tracts are sclerosed (Fig. 481), and there is a varying amount of diffuse degeneration in the anterior parts of the lateral columns. The changes in the pyramidal fibres, as a rule, start first and are most marked at their lower extremities, the process then extending upwards. Atrophic changes, corresponding to those in the anterior cornua, occur in the motor cells of the cerebral cortex and here also many disappear. It is to be noted too that the sclerosis of the pyramidal tracts may extend in the cord to a lower level than that at which the anterior cornua are implicated. It would appear that the two sets of neurons are affected independently by the same toxic agent, one or other being involved first and to a greater degree.

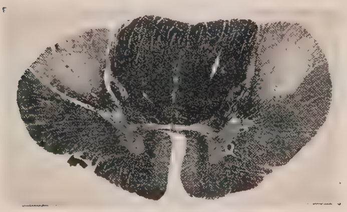


FIG. 481.—Section of Cervical Cord in Amyotrophic Lateral Sclerosis, showing Degeneration in crossed pyramidal and direct pyramidal Tracts. (Weigert-Pal method.)

There has been much dispute as to whether a pure *lateral sclerosis*, that is an affection of the upper neurons alone, occurs. In some cases of amyotrophic lateral sclerosis, lesions in the lower neurons are very slight and the symptoms are mainly those of involvement of the pyramidal tracts, that is, are of the nature of spastic paraplegia. But it seems doubtful whether the lower neurons are ever free from change, and a corresponding statement may be made with regard to the pyramidal fibres in progressive muscular atrophy. It may be noted that the symptoms of spastic paralysis may be produced by other lesions involving the pyramidal fibres, e.g. multiple sclerosis (p. 783), chronic myelitis and other transverse lesions. One form of the affection is known as Erb's syphilitic paraplegia. Such a condition, so far as the clinical symptoms are concerned, might be the result of syphilitic myelitis.

Bulbar Paralysis. In this affection, lesions occur in certain motor nuclei in the medulla, of a nature similar to those in the cord in the diseases just described. In fact, it is to be regarded as part of the same motor neuron disease ; in some cases it appears first, whilst in others it is a later stage of the spinal affection. The disease in the medulla is characterised by progressive paralysis and wasting of the muscles of the tongue, lips, jaws, larynx and pharynx; and death often occurs by involvement of the respiratory centre, or by foreign matter entering the lungs through the paralysed larynx. The lesions are essentially of the same nature as those in the cord. They are usually most marked in the hypoglossal and spinal accessory nuclei, but occur also in the nuclei of vagus and seventh nerves, and nucleus of motor part of the fifth. The oculo-motor nuclei are rarely involved. There is, of course, wasting of the corresponding nerves, and degeneration occurs in the corresponding upper neurons and their axons. Along with the changes in the bulb there is a varying involvement of the nerve cells in the anterior cornua, pyramidal fibres, etc. As stated above, nothing definite is known with regard to the etiology of these affections. There is also an acute form of bulbar paralysis in which the nuclei of the nerves mentioned are the seat of lesions produced by the virus of anterior poliomyelitis.

Subacute Combined Sclerosis

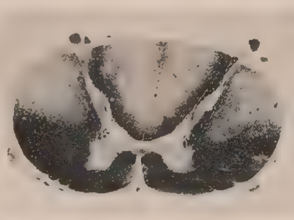


Fig. 482.—Section of Spinal Cord in a case of Combined Sclerosis, showing marked Degeneration in both lateral and posterior Columns.
(Weigert-Pal method.)

It has been recognised for some time that sclerosis of the cord, especially of the posterior and lateral columns, may occur in cases of pernicious anæmia; and similar lesions have been found in other chronic diseases, such as leukæmia, diabetes, and even in malignant disease. More recently, cases of such sclerosis have been observed without the presence of anæmia, and gastro-intestinal disturbance has been present in a considerable proportion of these. The term *subacute combined sclerosis* is now generally applied to such lesions. The etiology is still uncertain but it is believed by some that in pernicious anæmia the condition depends on the absence of a special neurotrophic factor in the gastric juice (p. 457). Another view is that deficiency of vitamin B_1 is concerned in its production, and favourable results have been announced from the administration of this vitamin. The anatomical changes are of distinct character, though varying in distribution; the long fibres in the cord are affected first, and both ascending and descending tracts are implicated (Fig. 482). The posterior columns may be degenerated in their whole extent, but there is no affection of the nerve roots. The pyramidal tracts, both crossed and direct, may be affected, but the degeneration tends to spread beyond them, especially in the dorsal region, where the disease is usually most extensive. In addition, there occur foci where the degeneration is more marked. In pernicious anæmia distinct disease of the cord occurs in about 5 per cent. of cases, though minor disturbances are met with more frequently. The degeneration in the motor tracts may ascend through the internal capsule and degeneration changes are met with in the Betz cells of the cortex. The appearance, accordingly, is as if there were a general toxic action, especially on the long fibres, with, in addition, a more intense action at certain places. There is no evidence that anæmia in itself produces the lesions mentioned ; as a matter of fact, it is usually preceded by them. The symptoms depend on the tracts involved. If they are mainly the posterior columns, ataxic symptoms are prominent, whilst affection of the lateral columns leads to spastic conditions. A combination of these main types may be met with ; ultimately there may be extensive paralyses.

The condition described by Gowers as *ataxic paraplegia*, corresponds with a combined sclerosis of the long fibres of the posterior columns and the pyramidal tracts, and probably belongs to the same group. Another example is met with in *pellagra*, a disease which is common in certain parts of southern Europe, and which is characterised by various skin eruptions, glossitis and diarrhœa, and also by nervous symptoms. It was for long ascribed to the eating of diseased maize, and was thus placed in the toxic group. It may now, however, be regarded as demonstrated that pellagra is due to a deficiency of vitamin B_2. This vitamin is a group of substances including lactoflavin, nicotinic acid and B_6 or adermin. The first and third have certain definite effects, but lactoflavin has been found to be the important substance so far as pellagra is concerned. Golberger showed that dogs fed on a B_2-free diet developed a condition known as ‘ black tongue,’ attended with glossitis and sprue-like changes, and that this could be promptly cured by nicotinic acid. Corresponding results have been obtained with pigs and monkeys. There has thus been afforded the means of assaying nicotinic acid. The administration of nicotinic acid in cases of pellagra has been followed by remarkable results. This has been confirmed by extensive trials in various places and opinion has been practically unanimous as to the curative effects. One can now say that absence or deficiency of nicotinic acid is the essential factor in the production of pellagra. Further, the curative effects of nicotinic acid in cases of malnutrition with minor nervous symptoms in this country make it likely that a mild form of pellagra is not uncommon. Deficiency in adermin, the third component of vitamin B_2, also known as vitamin B_6, produces a pellagra-like dermatitis in rats. To it the earlier results obtained on these animals by vitamin B_2 deficiency are apparently due. In cases of chronic *ergotism* somewhat similar changes are met with in the spinal cord, and these are apparently the result of toxins produced by the fungus in rye. The term *lathyrism* is applied to a disease met with especially in India amongst those of whose diet pulse forms an important part. It occurs sometimes in epidemics, males being much more frequently affected than females. The chief symptoms are those of a spastic nature affecting especially the extensor and adductor muscles of the lower limbs, but sensory symptoms also are present. The evidence points to affection of both lateral and posterior columns of the cord, but the exact changes are not definitely known. Stockman found that the disease is due to an alkaloid present in the peas of various species of Lathyrus. By feeding monkeys with the seeds of Lathyrus sativus he produced paralyses of muscles, which he considered were due to changes both in the peripheral nerves and in the spinal cord.

Disseminated or Multiple Sclerosis

This interesting disease is characterised by the presence of patches of demyelination sclerosis in the central nervous system. It occurs most frequently in early adult life, though cases are met with at both an earlier and later period. All observers are agreed that it is not of syphilitic origin, and while such conditions as various infective fevers, exposure to cold, excessive strain, etc., have been suggested as being related to the onset of the disease, nothing of this nature has been satisfactorily established. The disease is usually of slowly progressive character, while exacerbations, apparently due to the starting of new lesions, occur from time to time. Optic atrophy is sometimes met with.

Structural Changes. The sclerotic patches are scattered in an irregular manner throughout the spinal cord and brain. In the latter they occur especially in the lower parts—medulla, pons, crura, and thalami, and are comparatively rare in the upper parts of the hemispheres. They have sometimes been observed also in the cranial nerves and in the roots of the spinal nerves. On section of the affected areas, the sclerosed tissue is seen to have a greyish and rather translucent appearance, and forms a contrast to the healthy white matter from which it is sharply cut off. The grey areas vary in consistence, being sometimes firmer and sometimes less firm than the healthy tissue ; there is little or no contraction, and the configuration of the affected parts is well preserved. The patches are quite irregular in form and in distribution, affecting white and grey matter alike. They may appear as islets surrounded by healthy tissue, but sometimes the diseased tissue exceeds the normal in amount, and may surround surviving patches of the latter.

In sections stained by the Weigert-Pal method, one of the most striking features is the complete disappearance of the medullary sheaths in the affected areas, and the sharp line of demarcation from the adjacent healthy tissue ; on one side of the line the myelin appears quite healthy, while on the other side it has quite disappeared (Figs. 483, 484). Varying degrees of thickening of the neuroglia are present, but in recent patches there is little increase. The vessel walls are sometimes thickened and occasionally leucocyte infiltration may be present around ; on the other hand, the vessels may appear quite healthy, and it is not possible to relate the sclerosis to vascular disease. Such are the changes when the disease is well established, but at an early or active stage the demyelination may be less sharply demarcated and a certain amount of leucocytic infiltration may be present. A fact of great importance is that while the medullary sheaths are so extensively destroyed, the axis cylinders may persist, and may be capable of transmitting impulses for a long period. Accordingly, the sclerosed patches do not usually lead to secondary ascending or descending degenerations in the columns implicated. At a late period, however, there may be a certain amount of destruction of axis cylinders.

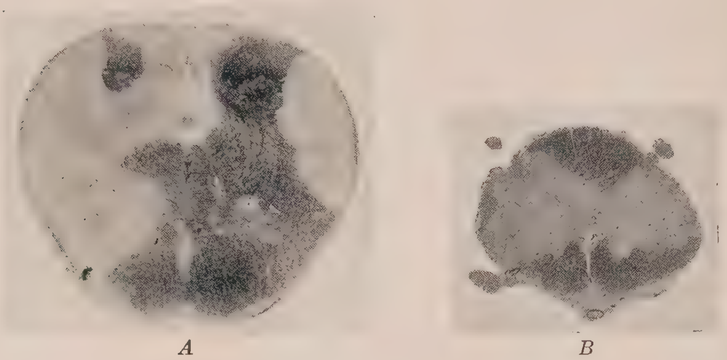


Fig. 483.—Multiple Cerebro-spinal Sclerosis.
(*A*) Section through lower part of medulla.
(*B*) Section through dorsal spinal cord.
The degenerated areas appear pale.
(Weigert-Pal method.)

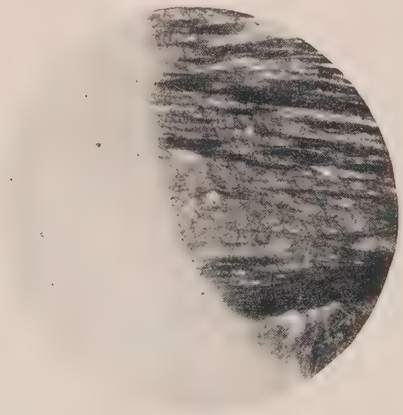


Fig. 484.—Margin of Sclerosed Patch in Cerebro-spinal Sclerosis, showing the sharp interruption of the Medullary Sheaths at the margin, the healthy tissue being on the right side. × 30.
(Weigart-Pal method.)

Nature of Disease. There seems to us to be no doubt that the primary lesion is one of the medullary sheaths and that the overgrowth of neuroglia is secondary. This is shown by the complete way in which the myelin is destroyed in a patch, and the sharp delimitation of the diseased from the healthy tissue ;

it would be hardly possible for neuroglial over-growth to produce such an appearance. Furthermore, in certain areas where the myelin has quite disappeared there may be little neuroglial overgrowth; and lastly, in such areas nerve cells and their processes may have a healthy appearance. It is now recognised that the primary and essential change is the process of demyelination, and in view of what is known of other diseases where this is the essential feature (p. 743) it is probable that the causal agent is a virus.

The *cerebro-spinal fluid* in multiple sclerosis may at times contain slight excess of lymphocytes, and there may also be increase of protein; but these changes are often absent. Lange's colloidal gold test often gives what is called a *paretic reaction*, similar to that met with in syphilitic affections. The Wassermann reaction, however, is negative, unless of course syphilis is present in addition. A paretic reaction in association with a negative Wassermann reaction is generally accepted as pathognomonic of multiple sclerosis.

The *effects of the lesions* on function vary much, as the disease is so irregular in its distribution, but certain features are usually prominent. The loss of the myelin sheaths interferes in some way with the conduction of the nerve fibres, and voluntary muscular movements take place in an irregular or jerky manner—the so-called 'intention tremors.' Transient diplopia, nystagmus and staccato speech are often present and are probably to be explained in a similar way. Often the sclerosis involves the pyramidal fibres, and thus a spastic condition of the lower limbs occurs. There are also not infrequently local paralyses, which may pass off to a large extent, and which are probably to be regarded as temporary pressure effects on the nerve fibres, when lesions start or become active; there may be a certain amount of accompanying pyrexia. As a rule there is no muscular atrophy, as the cells of the anterior cornua are intact, but in one very advanced case we found distinct atrophic changes in them.

Syringomyelia

The term is applied to a space or spaces in the substance of the cord, containing fluid and enclosed by neuroglia. The condition is to be distinguished from *hydromyelia*, which means a dilatation of the central canal of the cord. In hydromyelia the dilated canal is lined by the normal ependyma, but transitions to syringomyelia are met with. Hydromyelia is usually a congenital abnormality, but the accumulation of fluid is at times the result of pressure, e.g. by a tumour growth; it is sometimes met with in association with hydrocephalus.

Structural Changes. *Syringomyelia* occurs especially in the cervical region, though it may extend both to a lower and to a higher level, occasionally implicating the medulla; rarely, it affects the lumbar part of the cord. A point of importance is that it starts in the posterior part of the cord—behind the posterior commissure or in the base of one of the cornua, though the glial growth may extend more widely. The affected part of the cord is usually swollen in a varying degree and feels somewhat soft. Occasionally the growth of neuroglia is very great, almost reaching the character of a tumour, and in such a case a spindle-shaped swelling may fill the spinal canal at the affected part of the cord. On section, the appearances vary according to the amount of new tissue formed and the proportion of cavity formation. Thus, in some cases the lesion seems to be mainly a space, in others a glioma-like tissue with central softening; occasionally there appear to be more lesions than one, but in this case they are often found connected at intermediate levels. On microscopic examination, the tissue is seen to be gliomatous in type and fairly cellular, and it merges by a process of œdema and softening into the fluid in the spaces (Figs. 485, 486). At the periphery there is a greater proportion of glial fibres, and a considerable amount of interstitial overgrowth may extend into the structures of the cord around. When the condition is of moderate degree, its localisation in the posterior region of the cord can be made out, but when it is extensive this may be no longer discernible.

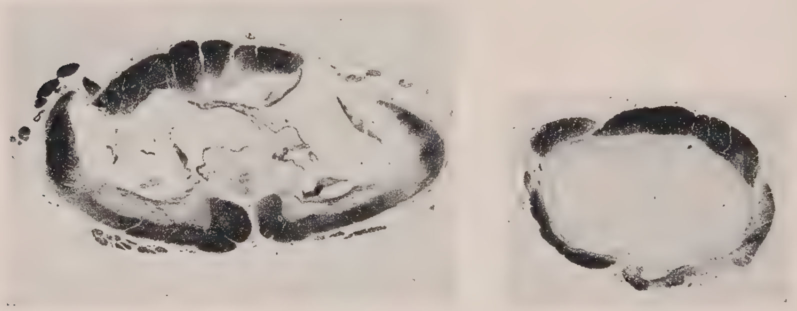


Fig. 485. Fig. 486.

Figs. 485 and 486.—Sections of Spinal Cord in a case of Syringomyelia, showing the central cavity at different levels, Fig. 485 being towards upper part of cervical enlargement and Fig. 486 towards its junction with dorsal portion. (Weigart-Pal method.)

Effects. The effects of syringomyelia are partly those of actual destruction of tissue and partly those of pressure. The sensory fibres specially apt to be interrupted are those which take origin in the posterior cornua and then cross in the posterior commissure to ascend in the antero-lateral ascending tracts. A curious disturbance of sensation ('dissociated sensation') results, so that while there is insensibility to pain and heat, sensibility to tactile impressions is retained, these being transmitted chiefly in the posterior columns. That the disturbance is due to a lesion of the decussating fibres, is shown by the fact that the area of disturbance of sensation corresponds in distribution to the segments affected by the syringomyelia; whereas if it were produced by interruption of tracts in their vertical course, it would affect all the body below the lesion. Motor disturbances occur also—both muscle atrophy from involvement of the anterior cornua, and symptoms of spastic paraplegia owing to implication of the pyramidal fibres. There is also an interesting series of trophic disturbances involving the joints, bones, and skin. The lesion of the joints is closely similar to that in tabes, but, as the syringomyelia is usually in the cervical region, it is the joints of the upper extremities which are chiefly involved, and the affection is often symmetrical. Atrophy of the bones occurs and spontaneous fracture may result. The trophic lesions of the skin are manifold, and the syndrome, known as Morvan's disease, in which the type of anæsthesia described above is associated with vesicles of the skin and painless whitlow, is just one manifestation of syringomyelia.

Nature of Lesion. There is no doubt that in the vast majority of cases, syringomyelia is of congenital origin. What probably happens is that in early embryonic life, the medullary canal is not completed posteriorly in the normal manner, and that neuro-epithelial cells become detached and embedded in the substance of the developing cord, and afterwards form neuroglial tissue. The spaces containing fluid are formed by an œdema and subsequent softening of the central part of the tissue, just as spaces are not infrequently formed in gliomata. It is possible that sometimes lesions like syringomyelia may result from hæmorrhage into the spinal cord occurring at birth, but such a source of origin is quite exceptional.

Caisson Disease or Diver's Palsy. When divers, or other workers in compressed air, e.g. in caissons, are brought back too quickly to ordinary atmospheric pressure, they may suffer from symptoms of weakness or paralysis, especially in the lower limbs ; and sometimes actual paraplegia may be present. The symptoms usually pass off, but some permanent results may remain. During the exposure to the high atmospheric pressure, the gases of the air become dissolved in increased amount in the blood and then in the tissues, and it has been shown by Vernon that the nitrogen is specially soluble in fats, including the myelin of the nervous system. The gases again become disengaged and are discharged by means of the blood stream, when decompression occurs ; but if it is carried out too rapidly, bubbles of nitrogen may form in the substance of the spinal cord. These bubbles occur specially in the white matter, as can be seen in sections, and this is apparently due to the fact that it contains fewer capillaries than the grey matter, by which the gas may be carried off, and also to its having absorbed more nitrogen. The bubbles produce symptoms by their pressure, and when they are ultimately absorbed the latter may disappear. Sometimes, however, areas of necrotic softening result, and this is believed to be due to blocking of capillaries with bubbles, which will not only interfere with nutrition but also with absorption of the nitrogen. Occasionally there is fat embolism (Fig. 23). The short period of time during which the nervous elements can withstand deprivation of blood is, of course, an important factor in bringing about the lesion. The occurrence of caisson disease may be entirely prevented by carrying out the decompression in suitably graduated stages.

TUMOURS OF BRAIN AND SPINAL CORD

Tumours of the central nervous system are of comparatively common occurrence and represent a great variety of types. Those in connection with the brain may be classified as: I. *Extra-cerebral tumours*, arising from the membranes or the sheaths of nerves; II. *Cerebral tumours proper*, arising from the brain tissue—in the vast majority of cases, from the neuroglia. A similar classification holds with regard to tumours of the spinal cord.

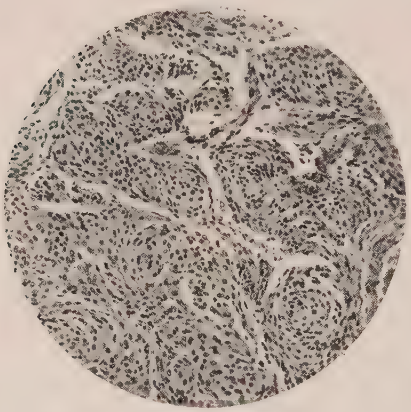


FIG. 487.—Section of Meningioma of common cellular type showing the arrangement of Cells and Fibres in Whorls. × 100.

I. Extra-Cerebral Tumours. The commonest tumour of this class is the *fibro-endothelioma* or *meningioma*, also known as psammoma, the characters of which have already been described (p. 211). The microscopic features of a somewhat cellular meningioma are shown in Fig. 487.

Meningiomas vary greatly in character, some being relatively hard or cretaceous, others being less fibrous and softer. In certain situations they may grow to a remarkable size before causing death, as illustrated in Fig. 488. They are well demarcated from the brain tissue and are, as a rule, of simple nature. For these reasons they are specially amenable to surgical treatment and can often be successfully removed. A not uncommon site is on the under surface of the brain between the frontal lobes (Fig. 489), where they originate in the region of the olfactory groove and cause characteristic symptoms, as described by Cushing. Not

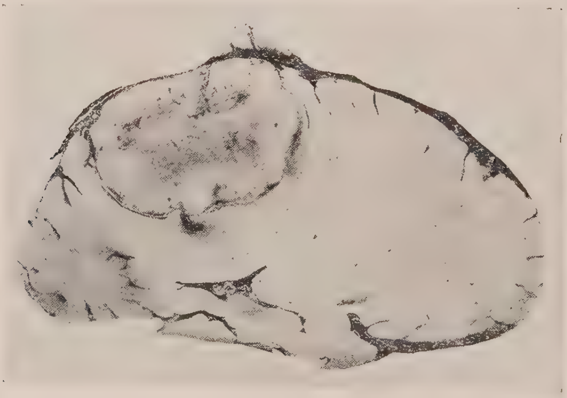


FIG. 488.—Large Meningioma in Vertex of Brain, bulging into the Hemisphere.

infrequently a meningioma gives rise to considerable thickening of the bone in relation to it. Occasionally it infiltrates the bone like a malignant growth but metastases do not occur. In such a case the cells have a considerable amount of cytoplasm and are arranged in masses, the characters of the growth corresponding with those of an endothelioma. The *spinal meningiomas* correspond in their general characters, but, owing to their situation, are of smaller size (Fig. 490). They are intradural growths which arise most frequently on the postero-lateral aspect of the cord, and the disturbances at first are chiefly sensory—pain, paræsthesia, etc. At a later period various effects up to complete paraplegia may result from pressure on the cord. A growth may have a comparatively slight basis of attachment and thus it may be readily removed.

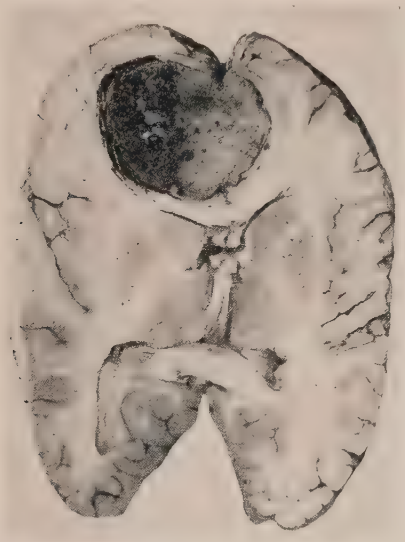


Fig. 489.—Large Meningioma between Frontal Lobes with Hæmorrhage in places.

Note that the growth is encapsulated and is simply displacing the brain tissue. × ½.

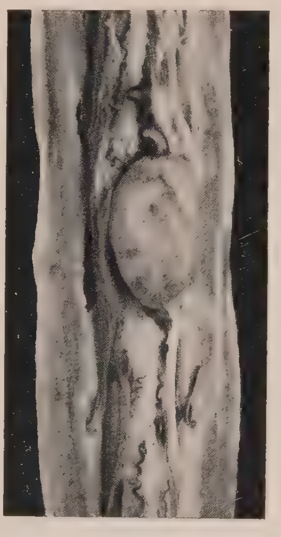


Fig. 490.—Meningioma growing from arachnoid and pressing on spinal cord. × ¾.

Meningiomas have usually been regarded as tumours of the dura, though it has been admitted that some take origin from the arachnoid. Recently, however, the view has been put forward that they are all derived from cells of the arachnoid, and the name *leptomeningioma* has been applied. So far as the naked-eye appearances go, we consider that some actually grow from the dura, whilst others, especially the larger ones, originate from the arachnoid, the dura becoming adherent to a varying extent. The two types of tumour are, however, of the same structural type, though those clearly growing from the dura are usually of harder consistence. In the normal dura there are often to be found small concentric bodies with central calcification resembling those in meningiomata, bodies from which the latter might conceivably take origin ; and the question is as to the source of these structures. Mallory, who believes that all fibro-endotheliomas are of arachnoidal origin, describes the occurrence of buds of proliferating cells on the surface of the arachnoid which pass into the substance of the dura, and considers that the dural endotheliomas spring from these. Learmonth has described a similar occurrence in the case of the spinal meninges, noting that the cells in question may form sand-bodies, and he comes to a like conclusion. It seems to us that the meningiomate constitute a single class and that they originate from cells of the arachnoid, either in that membrane itself or within the dura.

Another comparatively common intracranial tumour is a *neuro-fibroma* in connection with the sheath of the auditory nerve. It may come to form a mass of considerable size, somewhat nodulated on the surface, in the cerebello-pontine angle, where it sometimes produces a remarkable displacement of the parts (Fig. 491). Microscopic examination shows the growth to be composed of a fibro-cellular connective tissue of whorled or fasciculated appearance. At places the cells are closely arranged in a parallel fashion and, as the nuclei are often rod-shaped, a characteristic 'palisade' appearance results. (Fig. 492.) In addition to ordinary connective tissue and fibres, there is a considerable proportion of tissue of another nature, the cells and fibres of which stain a brownish-yellow tint with van Gieson's fluid. The latter cells are for the most part spindle-shaped, but some resemble neuroglial cells. Certain observers, e.g. Masson, consider that they are derivatives of neurilemma cells, and in accordance with this view the term *Schwannoma* has been applied to the tumour. Multiple neuro-fibromata occasionally occur on the nerve roots, both of the brain and spinal cord in cases of general neuro-fibromatosis (p. 803).

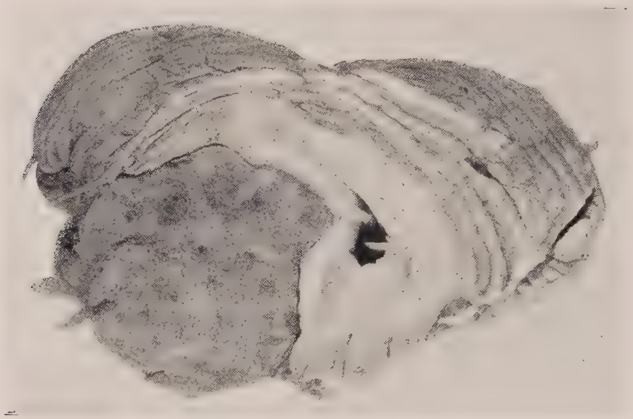


Fig. 491.—Large Tumour of sheath of the Auditory Nerve in cerebello-pontine angle, which has caused great displacement of the adjacent structures.

Tumours of vascular origin are of rare occurrence. Cushing and Bailey in their series found that they formed about 2 per cent. of cerebral tumours. They divide them into (1) angiomatous malformations which may be chiefly capillary, venous or arterial in constitution, and (2) the hæmangioblastomata or true neoplasms of blood-vessel elements. A peculiar syndrome in which one of the latter growths is present has been described by Lindau and is now known as 'Lindau's disease.' In this the vascular tumour, which is most frequently in the cerebellum, is composed of vascular channels or spaces, between which there is a large accumulation of lipoid-laden cells with a peculiar reticulum of fibres between them. There is a marked tendency to cyst formation ; transudation of fluid occurs into the tissue and forms a space or spaces containing fluid and lined with compressed neuroglia. In association with the growth there may be capillary angiomatosis in other parts of the nervous system and in the retina ; there are also lesions which are not of vascular nature—cysts in the pancreas (p. 645) or kidneys, and simple growths in the kidneys or adrenals.

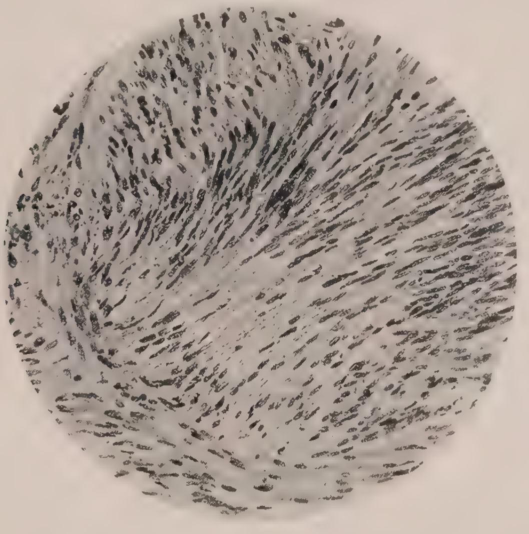


FIG. 492.—Acoustic nerve tumour, showing palisade arrangement of cells and other features. × 160.

Sarcomata sometimes arise from the membranes of the brain and present the usual features ; occasionally a growth extends widely over the surface of the brain. In some cases, however, these growths are really medulloblastomas which have invaded the meninges. Occasionally a primary *melanoma* occurs in connection with the membranes and forms a diffusely spreading growth.

II. Cerebral Tumours. The term is used in the strict sense to include all the growths which arise from the primitive medullary epithelium. The gliomata or tumours of the astroglia form the largest group, but there are growths which arise in connection with the ependyma and also rarer growths in which neuroblasts are concerned. Recent research on this subject dates from the publication of Bailey and Cushing's work and, though there is still uncertainty with regard to some points, there is general agreement as to the chief facts. A brief summary of these may be given.

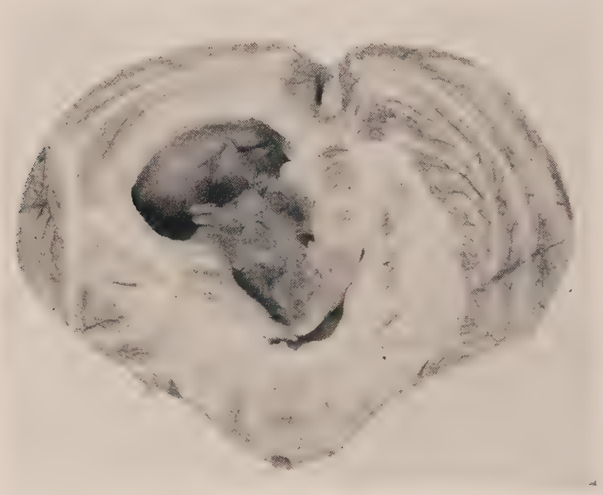


FIG. 493.—Glioma of right Lateral Lobe of Cerebellum with large space due to softening of the growth.

From the medullary epithelium three main cell types take origin, viz. (1) the primitive spongioblast, (2) the medulloblast, and (3) the neuroblast (some writers put a germ-cell as an intermediary between the last two types and the medullary epithelium).

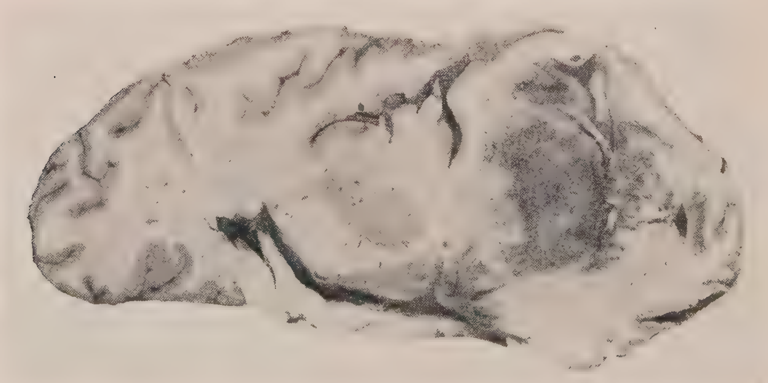


FIG. 494.—Spongioblastoma of Frontal Lobe.
Note the ill-defined margin and hæmorrhagic areas. × ⅔.

From the primitive spongioblast arise (*a*) the cells of the astroglia (ordinary neuroglia) and (*b*) the cells of the ependyma. The astroglia is formed through intermediate stages of apolar and polar spongioblasts and astroblasts, the adult cells being the protoplasmic and fibrillary astrocytes (p. 223). The ependymal cell has an ependymal spongioblast as its immediate predecessor. The medulloblast gives origin to the cells of the oligodendroglia and probably also to astroblasts and neuroblasts (opinion varies on this point). The neuroblasts are at first apolar, and then pass through the stages of polar neuroblasts to form the adult nerve cells or neurons.

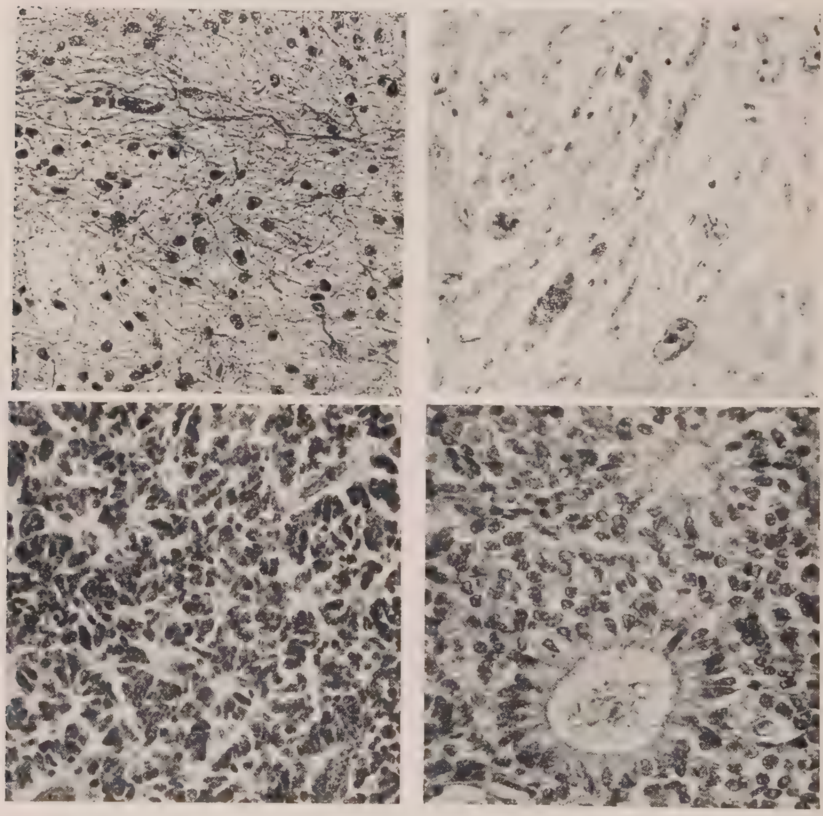
One may say that there are tumours corresponding in a general way to the various stages in the development of the cells mentioned, although, as might be expected, more than one stage may be represented in a growth. As in the case of other tissues, the general rule usually applies that the more primitive or undifferentiated the cells are, the more rapid is their growth. We shall give the characters of the three commonest growths, viz. astrocytoma, spongioblastoma and medulloblastoma, and mention briefly some of the others. These three growths constitute fully 80 per cent. of the tumours in Bailey and Cushing's series. The first two are undoubtedly the commonest and represent roughly the simple and malignant growths of the ordinary neuroglia, corresponding in fact to fibroma and sarcoma. The records with regard to the frequency of the two types vary somewhat. According to some (e.g. Bailey and Cushing) the astrocytoma is the commoner ; according to others, the spongioblastoma.

Astrocytoma. This was formerly known as the simple glioma. As described already (p. 223), it is a slowly growing tumour of whitish colour, badly defined at the margin where it merges with the surrounding nervous matter. The tumour often becomes œdematous and then undergoes softening, cyst-like spaces thus resulting. The cells are usually fibrillary astrocytes, but are often elongated or ‘ piloid ’ instead of being stellate. The amount of fibril formation varies much in different specimens (Fig. 495). The astroblastoma which is composed of cells of less differentiated type, is usually a somewhat softer and more vascular growth. It is, however, of less frequent occurrence.

Intermediate varieties are met with between a distinct tumour and a more diffuse overgrowth which may be called *gliomatosis*. The latter condition is found especially in the pons, where marked enlargement may result, although the structural arrangement of the pons may be well maintained. Gliomatosis occurs also in relation to the central canal of the spinal cord in connection with syringomyelia (p. 783). Apart from this condition glioma in the spinal cord is rare.

Spongioblastoma. The type cell is here the spongioblast which arises from the medullary epithelium. It is thus a primitive cell developmentally and the corresponding tumour or spongioblastoma is a rapidly growing, cellular tissue ; it may be said to correspond to the sarcoma of ordinary connective tissue. The commonest type is characterised by great variations in cell characters and is accordingly called *spongioblastoma multiforme.*

This tumour is met with usually about middle life and occurs most frequently in the cerebral hemispheres, where it often forms a large mass. The tissue is somewhat soft and vascular and is often the seat of hæmorrhages and necrosis. A certain amount of condensation of tissue may be present at the margin and give the deceptive appearance of a capsule being present. The effects of the growth are those both of destruction and of pressure. Its cells are of great variety in size and in shape, oval, spindle-shaped, etc., and very often they are of large and of irregular form, with aberrant nuclear characters (Fig. 496). Mitoses are comparatively frequent. A common



[1] Figs. 495–498.—Types of Cerebral Tumours. × 225

Fig. 495.—Astrocytoma.
Fig. 496.—Spongioblastoma multiforme.
Fig. 497.—Medulloblastoma.
Fig. 498.—Ependymoma.

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[1] I am indebted to Dr. J. W. Kernohan for a loan of the sections from which Figs. 497, 498 were taken.

feature is the presence of solid bud-like or ' glomeruloid ' growths of endothelial cells projecting from the vessel walls. The histological picture may vary at different parts and there may be at places a considerable number of astrocytes ; these may possibly represent in part a reactive formation. Spongioblastomas are occasionally met with in which the cells have one or two processes and are called unipolar and bipolar spongioblastomas. These represent growths from cells more differentiated and older in ontogenetic development.

Medulloblastoma. The medulloblast is another cell which develops from the medullary epithelium ; its relationships have been stated above. Like the spongioblastoma the medulloblastoma is a rapidly growing, cellular tumour. Its cells in places are spherical in form with little protoplasm, resembling those of a round-celled sarcoma, and there are no fibrils. In other parts the cells are somewhat triangular, like short carrots ; they tend to be arranged round blood-vessels and also as circles or rosettes without central cavity (Fig. 497). The medulloblastoma occurs especially in children and a common site is the fourth ventricle, where it forms a cellular mass. It is met with also in adults and occasionally extends to the meninges where it forms a diffuse spreading growth like a sarcoma.

Ependymoma. This is a rare tumour met with most frequently in the fourth ventricle, though also in the other ventricles and in the spinal cord. The type cell is elongated with a single tail and the growth contains many fibrils. At places the cells are distinctly of ciliated columnar type and line spaces (Fig. 498) ; near the base of the cilia there may be small rod-shaped ' blepharoplasts.' The *ependymoblastoma* is a less differentiated type. Another form of ventricular growth is the *choroidal papilloma.* It has a distinctly papilliform structure, being composed of a vascular connective tissue core covered by columnar epithelium. It grows slowly but produces pressure effects.

Oligodendroblastoma. This is a very cellular growth occurring chiefly in the cerebral hemispheres. It is, however, more slowly growing than the spongioblastoma or medulloblastoma and not infrequently there is calcification at places. The cells are small and rounded like those of the oligodendroglia, with somewhat clear protoplasm, and the processes are small and difficult to demonstrate.

Neuroblastoma and Gangliocytoma. These constitute a class of rare but very interesting tumours. Tumours composed of primitive nerve cells are commoner in connection with the sympathetic system (p. 255). The type cell is the neuroblast and it is seen at different stages of development. The nucleus is of vesicular type with a distinct nucleolus and in more adult types of growth there may be formation of Nissl's granules and dendrites in varying degree. The rate of growth of such tumours varies according to the stage of development of the cells.

Several cases have been recorded in which multiple tumours of neuroglia and nerve cells have occurred in the cortex of the brain, in association with rhabdomyoma of the heart muscle (p. 371) and other congenital abnormalities.

Cholesteatoma is an interesting type of growth which is occasionally found in connection with the membranes, especially at the base of the brain. It is usually well encapsulated, and its substance has a whitish and rather glancing appearance and a somewhat crumbling character. It is composed of cells of epithelial type arranged in whorls and containing crystals of cholesterol. It was at one time believed to take origin from the endothelium of the arachnoid, but there is little doubt that it is of epidermoid origin and represents a congenital abnormality. In some instances hairs and sebaceous glands have been present. *Teratomata* have occasionally been found at the base of the brain, especially in the region of the pituitary, but they are of rare occurrence.

Secondary growths, both sarcoma and carcinoma, are met with in the brain but are not common. An extensive secondary invasion of the brain by melanotic growths is sometimes observed. The cells of the growth have a great tendency to spread along the perivascular lymphatics, so that vessels, including even the capillaries, may be ensheathed by them.

EFFECTS OF TUMOURS. Intracranial tumours produce both local and general effects. By pressure on the motor areas they may give rise to symptoms of irritation leading to spasms and convulsions. Or again, paralysis may be brought about by pressure on or by actual destruction of the nerve cells and fibres. A growth of considerable size leads to increase of the contents of the cranial cavity, and thus the convolutions become flattened and symptoms of compression result. Another result is that owing to the pressure above, the medulla along with the adjacent cerebellar tissue is pushed down into the foramen magnum and forms a sort of cone-shaped plug or 'pressure cone.' In this way the cranial cavity would appear sometimes to be quite shut off from the spinal canal. A tumour occurring below the tentorium very often presses on the aqueduct of Sylvius or fourth ventricle, and thus leads to hydrocephalus (p. 733). This condition may also be produced by a tumour at a higher level exerting pressure on the foramina of Monro or on the third ventricle. Occasionally unilateral hydrocephalus may result from occlusion of one foramen of Monro. The occurrence of optic neuritis or papillœdema is a common result of cerebral tumours. It is apparently produced in a mechanical way, the cerebro-spinal fluid, owing to the increased pressure, being passed along the sheath of the optic nerve ; thus the venous return is interfered with, and the disc becomes engorged and then œdematous, the condition also known as 'choked disc' thus resulting.

CONGENITAL ABNORMALITIES OF THE BRAIN AND SPINAL CORD

Brain. Defects of the brain are of considerable variety and the anatomical changes are often of a complicated nature ; we can only summarise the main facts. *Anencephaly* is a condition in which there is deficiency of the cranial vault with absence of brain, although there is often a small sac with remains of cerebral tissue on the exposed base of the cranial cavity, the base also being deficient in size. The condition, which is incompatible with life, is not infrequently associated with non-closure of the spinal canal or *rhachischisis.*

Occasionally there is a deficiency in the cranial bones and a sac-like protrusion is present. This occurs in the line of a suture, is often mesial in position and as a rule posterior ; or it may be lateral, e.g. at the side of an orbit or the nose. The sac is lined in some instances by the membranes of the brain and contains merely cerebro-spinal fluid ; the term *meningocele* is then applied. In other cases the sac is filled by brain substance, and sometimes when the defect is posterior, may contain a considerable part of the cerebrum ; the condition is then known as *encephalocele.* The term *micrencephaly* means a congenital smallness of the brain. There is deficiency in the convolutions, and the sulci, especially the secondary, are imperfectly marked ; the state is associated with a greater or less degree of idiocy. The whole brain may be deficient, but as a rule the cerebellum and lower parts are less affected than the hemispheres. Sometimes again, there is a local defect in growth, often associated with a small size of the convolutions or *microgyria.* There is no doubt that micrencephaly is a primary defect in the growth of the brain, though its cause is not known, and it is not due to closure of the sutures, as was once supposed. The term *porencephaly* is applied when part of the brain substance is wanting, its place being taken by a collection of fluid. The space is covered by the membranes of the brain, and it sometimes communicates with the ventricles. Two varieties of the condition are distinguished, namely, a primary or developmental form and a secondary. In the former, the defect is due to failure of growth or *agenesia*, and the edges of the space are usually smooth. Such a condition is occasionally bilateral and is sometimes associated with other abnormalities. In the secondary form, the lesion is supposed to be the result of encephalitis or of interference with the blood supply during intra-uterine life, and a somewhat similar condition may result from injury at the time of birth. The most common abnormality, namely, hydrocephalus, has been considered above (p. 732).

Spinal Cord. Non-closure of the spinal canal or *rhachischisis*, is sometimes met with, especially in the lower part of the cord, and is often associated with anencephaly, but a more common and important condition is one in which there is a local deficiency in the arches of the vertebræ, whilst the opening is covered posteriorly by soft tissues. The term *spina bifida* is applied to such a condition ; a distinct rounded projection is usually present over the site of the defect and then we speak of *spina bifida with tumour.* When there is no such projection the term *spina bifida occulta* is applied.

The commonest position of spinabifida is in the lumbo-sacral region, and in all cases the spinal cord extends to a lower level than the normal ; in other words, it occupies a position which occurs in the earlier stages of development. The cord and membranes are variously disposed in different cases. In the commonest form, the spinal cord is adherent to the posterior wall of the sac and the term *myelomeningocele* is applied. The dura mater is absent in the sac, and at the apex of the latter there is often an area where the skin is deficient. At this point there is a smooth tissue in which the spinal cord is incorporated, the cord being open posteriorly, and sometimes one or two small depressions are present, the latter indicating the upper and lower terminations of the central canal. The spinal nerves are spread out on the inner lining of the sac. In another form, the space containing the fluid is a distension of the central canal of the spinal cord and is lined by the epithelium of the ependyma. In this variety, which is called *myelocystocele* or *syringomyelocele*, the spinal cord has been closed in posteriorly, and thus the abnormality has arisen at a later period of development than the previous form. In a third variety, which is the least common, the sac is lined by a hernial protrusion of the arachnoid, whilst the spinal cord is in its normal position in relation to the vertebræ. This is called *meningocele.* In all three varieties the dura mater is absent locally. The contents of the sac in spina bifida are cerebro-spinal fluid. In the first variety, the fluid is in the subarachnoid space in front of the spinal cord ; in the second, it is in the dilated canal of the cord, and in the third, it is in the subarachnoid space behind the cord.

In *spina bifida occulta,* where there is no swelling to indicate the defect, the skin over the part usually shows abnormalities in appearance, and not infrequently there is excessive growth of hair. Here also, the cord extends to a lower level in the spinal canal than normally. Abnormalities in connection with the central canal have already been described (*vide* syringomyelia, p. 783).

THE NERVES

Neuritis

Under the heading of neuritis there are included affections which fall into two main categories. In the first, the essential change is a degeneration of the nervous elements which is attended by little or no inflammatory reaction in the interstitial tissue. Such a lesion is, to speak generally, the result of toxic action, the poison being distributed by the blood stream ; in accordance with this, many nerve branches are affected together and in a more or less symmetrical manner. The term *multiple peripheral neuritis* or *polyneuritis* is usually applied to disease of this type. In the second category, we have to do with local affections of nerves, and the primary change would appear to be usually in the interstitial connective tissue and of the nature of an acute inflammatory condition with exudate, though primarily subacute and chronic interstitial forms also occur. The affection is thus asymmetrical and is due to some local determining condition. There is to be considered also the type of neuritis which occurs in beri-beri, where the primary cause is not a toxin acting from without but a deficiency of a vitamin in the diet. We shall now consider these types more in detail.

Multiple Peripheral Neuritis. This is known also as *parenchymatous neuritis*, in view of the elements affected, or as *toxic neuritis* in view of its causation. The poisons which may produce degenerative changes in nerves are very numerous. They may be divided into three groups.

(*a*) *Inorganic poisons*, such as arsenic, antimony, lead, silver, etc.

(*b*) *Organic poisons of known constitution*, such as alcohol (the commonest cause), ether, dinitrobenzol, carbon bisulphide, etc. ; possibly the neuritis which occurs in diabetes is due to a body of this class, though there is also the possibility that it is due to a bacterial toxin, as infections are so common in this disease.

(*c*) *Organic poisons of unknown constitution, or toxins.* These are chiefly of bacterial origin, and accordingly neuritis is a common result of infections and specific fevers. Thus neuritis, especially of the cranial nerves, is a fairly common sequel of diphtheria, giving rise to post-diphtheritic paralysis. It can also be produced experimentally in animals by injection of the toxin. Neuritis may follow influenza, typhoid, smallpox, acute rheumatism, gonorrhœa, and various septic conditions, notably puerperal infection ; it is occasionally met with in tuberculosis and as a sequel to malaria. As a general rule, in all these conditions it is the small nerve twigs which are affected first and in greatest degree ; the affection diminishes in an upward direction and the main trunks may be free from change. In some instances, evidence of toxic action on the tracts of the spinal cord has been found in peripheral neuritis.

Alcoholic neuritis is a not infrequent variety, is usually caused by spirit-drinking, and occurs much more frequently in women than in men. It is now less common than it used to be. Whilst it has generally been ascribed to alcohol *per se* recent work has shown that vitamin B_1 deficiency, which causes the polyneuritis of beri-beri, may be concerned in its production. There may be a deficient intake of the vitamin in the food, or more probably a deficient absorption from the alimentary canal owing to gastro-intestinal disturbance. Parenteral administration of the vitamin in cases of alcoholic neuritis has been attended with favourable results. A wide field has thus been opened up, and it is possible that in other forms of neuritis, e.g. that of diabetes, deficiency of this vitamin may play a part. In alcoholic neuritis the nerves, on naked-eye examination, may show no alteration, but we have found that in long-standing cases the smaller branches may have a slightly yellow tint and may be flabby to the touch and of softer consistence than the normal; this alteration apparently occurring when the degenerated myelin has been in part absorbed. The primary change seems to be in the medullary sheaths; the myelin becomes broken up into globules which give the Marchi reaction (p. 141), and these then undergo absorption. The neurilemma cells become swollen and act as phagocytes of the fatty material, which is taken up also by leucocytes and other cells. Many of the axis cylinders become bare; they show irregular swellings and varicosity, and are broken across (Fig. 499). There may be little or no evidence of inflammatory reaction in the connective tissue beyond the presence of a few leucocytes. Later, regeneration of the axis cylinders may occur, but this is often interfered with by persistence of the toxic action. Proliferation of the interstitial connective tissue cells then takes place, and fibrosis with permanent loss of nerve fibres follows. The muscle fibres in relation to the interrupted axons undergo fatty or granular degeneration; the sarcolemma cells proliferate and degenerated material becomes absorbed. If there is restoration of the nerve supply the sarcous substance may be regenerated by the sarcolemma cells; if not, then permanent atrophy with interstitial thickening is the result.

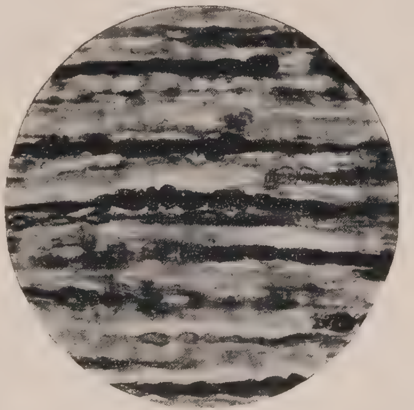

Fig. 499.—Longitudinal section of Nerve in Alcoholic Neuritis, showing changes in medullary sheaths and axis cylinders. Stained with osmic acid. × about 250.

Apart from the tenderness along the nerves and a varying amount of pain, the effects of polyneuritis are chiefly those of interruption of the nerve fibres. Thus there occur anæsthesia, paralysis and wasting of muscles, inco-ordination, disturbance of the reflexes, trophic disturbances, etc.

Acute Interstitial Neuritis. This, as has been stated, is due to some local cause, and is asymmetrical in its distribution, though sometimes several nerves are affected. It follows exposure to cold and wet, especially in the gouty and rheumatic, but the mode of action of exposure is not properly understood. It results also from such conditions as septic wounds, bed-sores, diseases of joints, phlebitis, etc., and the toxins sometimes extend along the nerve sheaths and produce their effects for a considerable distance. The affected nerves become swollen and congested, and their connective tissue is the seat of inflammatory exudation, chiefly of a serous character. Leucocyte emigration is usually not pronounced, unless when pyogenic organisms are present. In some cases the exudation is chiefly into the sheath of the nerve, in others the interstitial tissue proper is affected. In the latter case the nerve fibres, especially the medullary sheaths, become degenerated, but not to the same extent as in multiple neuritis, since the affection of them is of secondary nature. Many of the symptoms are due to pressure of exudate and disappear when the latter is absorbed, but sometimes there may be permanent loss of fibres with corresponding wasting of muscles.

Interstitial neuritis may also be *chronic* from the outset. A striking example of this is seen in leprosy, where the bacilli enter the supporting sheaths of the nerves, and give rise to interstitial growth of connective tissue followed by atrophy of nerve fibres, paralytic and trophic disturbances then resulting. Interstitial neuritis may be produced also by syphilis, notably in the cranial nerves at the base of the brain, and in any form of meningitis the inflammatory change may spread to and affect the emerging nerves or roots. There is described also a senile form of chronic neuritis, in which there is sclerosis of the interstitial tissue with involvement of the nerve fibres. This is the result of advanced arterial disease, which interferes with the blood supply and causes a sort of fibrous atrophy.

Beri-beri. In this disease the essential lesion is a polyneuritis, which is the result of the absence or deficiency of an accessory food principle, and is usually caused by a diet consisting too exclusively of over-milled cereals, especially rice. The disease, which is met with principally amongst rice-eating populations, occurs in two forms. In one—the ‘ dry ’ form—the peripheral nerves are chiefly affected and there occur the usual symptoms of anæsthesia, wasting, and ultimately paralysis of the muscles, etc. In the other, or ‘ wet ’ form, the disturbances are mainly cardiac ; the heart becomes dilated, especially the right ventricle, there is general venous congestion, and dropsy usually becomes a marked feature—hence the term applied. The changes in the nerves are essentially parenchymatous and of degenerative nature like those in toxic neuritis. The myelin sheaths become degenerated and give the usual reactions, whilst the axis cylinders become irregularly swollen and interrupted in their continuity. Degenerative changes have been found also in the cells of the spinal cord and root ganglia. In the wet form we have found degenerative changes in the vagi and phrenics, and this has been the common result; degeneration has been noted also in the sympathetic system. It is likely that the cardiac dilatation is secondary to the lesions in the nerves, but the possibility of a primary change in the cardiac muscle cannot be excluded. Polyneuritis can readily be produced in fowls and pigeons by feeding them with milled or polished rice; and these animals, especially pigeons, have been largely used in studying the distribution of the anti-neuritis vitamin, now known as vitamin B_1. One of the most remarkable points about the experimentally produced disease, is the rapidity with which recovery takes place when the birds are fed with substances containing the necessary vitamin. Polyneuritis has been produced also in the rat by deprivation of vitamin B_1, but the changes are less constant and less marked. These facts have been applied to the treatment of beri-beri. Substitution of under-milled for milled rice has caused beri-beri to disappear in many places and the various facts ascertained establish the importance of vitamin B_1. The wet form of beri-beri has been ascribed to deficiency of protein in addition. Vitamin B_1 has now been isolated from rice polishings in a pure crystalline form; it has also been synthesised. It is called *aneurin* in Europe on account of its antineuritic properties but in America it is known as *thiamin*. The vitamin B_1 content of various foods has now been estimated (*vide* infra). Apart from actual beri-beri a condition of hypovitaminosis B_1 characterised by malnutrition is commoner than was supposed, especially in children. It is probable also that the deficiency plays a part in alcoholic neuritis, as this has been found to be relieved by parenteral administration of vitamin B_1. As in other conditions of hypovitaminosis, the condition may be due to deficiency of the vitamin in the food or to defective absorption owing to gastro-intestinal disturbance. In subacute combined degeneration of the cord, too, favourable results have been obtained by treatment with vitamin B_1.

Vitamin B_1 is widely distributed and is abundant in cereals and pulses. Chick and Hume showed that in the former it is most concentrated in the embryo or germ, and is fairly abundant in the bran (consisting of pericarp and aleurone layer of endosperm) which is removed by milling; whereas it is practically absent from the rest of the endosperm, of which wheat flour and polished rice consist. It is abundant also in yeast and fairly abundant in egg-yolk and ox liver, whilst it is scanty in milk and meat. Vitamin B_1, in contrast to Vitamin C (p. 486), is a relatively stable and resistant substance; it is unaffected by drying and withstands boiling, but is gradually destroyed at 120° C.

Regeneration of Nerves

Few questions in pathology have been the subject of so much dispute as the mode of nerve regeneration. According to one view, when a nerve is cut across or its fibres are destroyed, the formation of new axis cylinders occurs only from the central end. Thus, in conformity with the neuron conception, the axon is part of the nerve cell and can be formed only by the latter ; it cannot be produced by other cells, e.g. neurilemma cells, and then become united with the nerve cells. The other view is that in the distal or peripheral part regeneration occurs up to a certain stage through the activity of the neurilemma cells, and becomes complete when continuity with the central portion is restored. This latter view received strong support from various authorities some years ago, but at present the preponderance of opinion is in favour of the central mode of regeneration.

If we take as an example simple transverse division of a nerve, it is found that the changes which follow are very different in the two parts. In the *proximal* part there is degeneration of the myelin for only one or two segments above the lesion, this being in marked contrast with what occurs in the distal portion. At a very early period the proximal ends of the interrupted axis cylinders become swollen and split up into their fibrils, which rapidly increase in length and spread outwards in the tissue beyond. They often present bulbous extremities, and they run in an irregular curling fashion until they reach the distal part of the nerve, where they pass longitudinally in the spaces formerly occupied by the nerve fibres. Accordingly, the advantage of bringing the cut ends accurately into apposition is apparent, as in this way the new fibres are more rapidly guided to the periphery. It may be mentioned that when there is a gap between the two ends and a portion of nerve is transplanted, the latter serves merely as a guiding path for the new fibres to the distal part of the nerve. According to the view of regeneration from the central end, all repair is effected by the growth of the young fibres along the distal segment to the periphery, and requires some months for its completion ; although the time will, of course, depend on the distance of the lesion from the peripheral terminations. The young fibres are accompanied by neurilemma cells, and at a later period new medullary sheaths are formed around them.

The new growth of fibres is often exemplified in a striking way at the ends of cut nerves in cases of amputation. Here the new fibres run in an irregularly coiled fashion, and the accompanying growth of connective tissue around, often leads to the formation of a bulbous swelling at the end of the nerve—the so-called *amputation neuroma* (Fig. 500).

In the *distal* portion, Wallerian degeneration occurs in all the nerves which have been separated from their neurons. The initial change is in the axis cylinders, which become irregularly swollen and varicose, break into globules, and are thereafter gradually absorbed. This is probably of the nature of an autolytic change, and is readily understood according to the view that an axon is really part of a nerve cell and not simply formed material. Degeneration in the medullary sheaths accompanies that in the axons, the myelin breaking up into fatty globules, which can be demonstrated by Marchi's method. At the same time the neurilemma cells become swollen and proliferate, and act, along with leucocytes, as phagocytes in taking up the myelin globules. The next process is a gradual absorption of the degenerated material, which occupies a considerable time. After this has been completed, the neurilemma cells are seen to form parallel lines, and when the young nerve fibres grow along the sheath from the central end, they take a part in the formation of new medullary sheaths and thus in the completion of the process of repair. It is likely that the degenerated myelin exerts a chemotactic or neurotropic effect on the young nerve fibres, guiding them in their course. According to the peripheral view of regeneration, the neurilemma cells by differentiation of their protoplasm, lay down small axis cylinders and even myelin around them, in short, new nerve fibres; but these remain of small size and in an undeveloped condition until union with the proximal end of the nerve occurs. They then grow to full maturity.

In support of the latter view it has been held that return of function after a nerve has been sutured, and especially the early return of sensation after secondary suture, may take place too rapidly to be due to regeneration in the peripheral segment. Kennedy found that when the sciatic nerve of the dog was divided and thereafter sutured, power of movement began to return on the seventh day and was completely restored at the end of three weeks. He further made the interesting observation that voluntary co-ordinated movements were regained equally well whether the two ends were united in the original position, or the peripheral segment was twisted so as to disturb the relative arrangement of the fibres as much as possible. He also crossed the nerve supply of antagonistic groups of muscles, uniting the peripheral ends of nerves supplying flexors with the central ends of those supplying extensors, and vice versa; in this way extensor muscles were connected with a flexor centre in the cortex. Nevertheless, naturally co-ordinated movement was regained

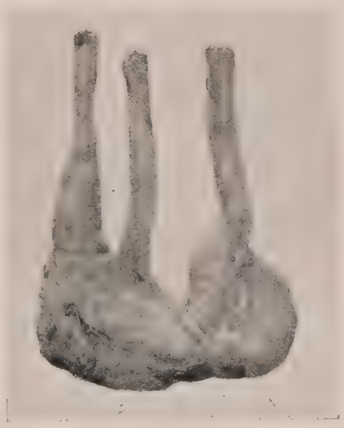

Fig. 500.—Amputation Neuromata at lower end of Nerves of Arm.

within three months. The power of adjustment to new nervous connections is thus very remarkable.

Tumours

These take origin from the connective tissue of nerves—hence often called 'false neuromata'—and are of various types. They are usually fibromata, but occasionally myxomata, and a myxoma may reach a large size and undergo central softening; lipomata also have been met with. Neuro-fibromata may occur as isolated single nodules, rounded or fusiform in shape, or there may be several. The nerve fibres may be spread over the surface, especially at one side, but are not incorporated in the tumour. The term *perineural fibroma* is often applied; the tumour of the acoustic nerve (p. 788) is an example. To speak generally, such growths may be said to be fibro-cellular tumours, the cells being arranged in bundles or whorls. The characteristic palisade arrangement of nuclei described in connection with the acoustic nerve tumour is often seen, but sometimes it is absent. Such growths have usually been believed to arise from the cells of the endoneurium or perineurium but Masson, as the result of experimental enquiry and observations on human examples, holds that they originate from neurilemma cells. If a portion of nerve is removed and then a transverse incision be made at the proximal end of the distal portion a tumour-like growth arises from the portion of nerve thus isolated. He found that the neurilemma cells proliferate and form a syncytium, the nuclei of which divide in a parallel manner and give rise to the palisade appearance. Division of the cytoplasm then follows and collagen is formed between the individual cells. This last occurs under the influence of the neurilemma cells, and according to Masson the only mesoblastic collagen present is that in relation to blood vessels. The terms *Schwannoma*, *neurinoma* or *peripheral glioma* have been applied by supporters of this view. Certain appearances lend support to it, but the matter cannot be regarded as settled. Neuro-fibromata are of all degrees of cellularity and the development of sarcoma in con-

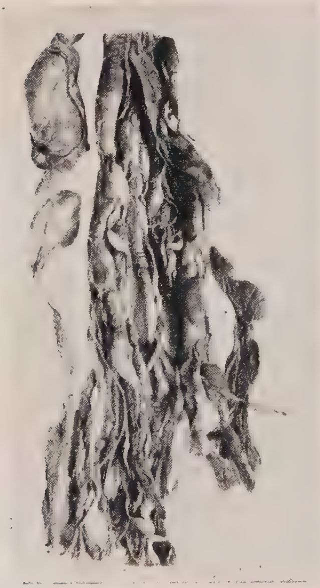

Fig. 501.—Diffuse Neuro-fibromatosis of Sciatic Nerve and its Branches.

Note the numerous nodules of various sizes and forms.

nection with them is not uncommon. Sarcoma sometimes arises in connection with comparatively large nerves, e.g. the posterior tibial, and the real origin of the growth is sometimes overlooked.

In other cases, a group of nerves, a plexus, or the sciatic and its branches, may be affected generally, and show numerous irregular thickenings with oval or beadlike swellings in their course (Fig. 501). Then there is the form known as the *plexiform* or *racemose* type, where the nerves of a region, usually the scalp or the neck, are the seat of tortuous thickenings which often give rise to firm elevations with somewhat convoluted appearance. Further, there is the condition of general neuro-fibromatosis ('von Recklinghausen's disease'), where nodules of various sizes, sometimes numbering hundreds, occur along the small branches, especially of the skin, but also in some cases along the visceral branches of the sympathetic. In this disease, nodules are sometimes met with also on the spinal nerves and their roots, within the spinal canal. The connective tissue of the nodules varies in character but is often of dense hyaline nature ; nerve fibres can be traced running through it at places. It is interesting to note that, as mentioned in a previous chapter (p. 251), neurofibromatosis is often associated with multiple pigmented nævi and there is strong evidence that the latter originate from the peripheral terminations of sensory nerves. Lastly, there may be occasionally a localised condition of great general thickening of the tissues, with nodulation and folding of the skin—a sort of local elephantiasis.

CHAPTER XVIII

LOCOMOTOR SYSTEM

A. BONES

Introductory. Although osseous tissue is hard and comparatively unyielding, it is in pathological conditions eminently subject to changes in compactness and also in configuration. It is generally recognised that in the normal state processes of formation and resorption are constantly going on ; in the adult these changes are normally balanced, but if either is interfered with, the character of the bone will become altered. Maintenance of the size and consistence of a bone is markedly dependent upon the functional requirements of support in response to pressure and tension, brought about by muscular action. Thus muscular inactivity is followed by atrophic change in bone, whilst special stress, as occurs in very muscular subjects, leads to increased strength and prominence of the ridges for the attachment of muscles. Even when there is widespread disease of bone, e.g. in rickets and osteomalacia, we find an adaptive thickening of bone where there is special strain or stress.

Bones are liable to various organismal infections (suppuration, tuberculosis, and syphilis, being the chief), and in these we find effects and reactions very similar to those seen in the soft tissues. In fact, if we consider osseous matrix as corresponding with fibrous matrix, we find a close parallel between the two kinds of tissue. Thus when an inflammatory condition is accompanied by an abundant overgrowth of granulation tissue in relation to bone, the latter undergoes absorption and the term *rarefying osteitis* is applied ; when the condition is of more chronic character, such as would be accompanied by fibrosis in a soft tissue, the bone becomes increased in amount and in density—*formative osteitis*. Necrosis of bone, that is, of its cells, may be produced by any of the chief causes already mentioned. The dead bone, if aseptic, may be absorbed or become encapsulated by sclerosed bone, or, on the other hand, if pyogenic organisms are present, inflammatory reaction with suppuration occurs around. Dead bone, owing to its physical characters, is, of course, removed slowly and requires for its resorption the action of living tissues in contact with it ; bone bathed in pus, for example, undergoes little or no resorption.

The growth of bone is definitely related to some of the *endocrine* *glands.* Thus the secretion of the anterior lobe of the pituitary stimulates in some way the growth of bone ; when in excess in early life it leads to giantism, when deficient to a dwarfed condition of the body. Thyroid secretion has a somewhat similar effect ; deficiency at an early age results in the stunted growth of sporadic cretinism, and in this condition the administration of thyroid extract often leads to considerable growth. On the other hand the parathyroid hormone has an important action in leading to absorption of lime salts from the bones ; when it is present in excess in the blood important structural changes are brought about (p. 834). It is quite likely that certain general diseases of bone, whose etiology is still obscure, may depend upon disorders of the endocrine glands. Bone is also under the trophic control of the *nervous system,* and important changes of an atrophic and dystrophic nature occur in chronic nervous diseases, notably in locomotor ataxia and syringomyelia. Again, in the case of scurvy, especially in infancy, very marked changes, as will afterwards be described, occur as a result of deficiency of vitamin C ; and recent experimental work has shown that the characteristic changes of rickets are produced by deficiency in vitamin D.

Atrophy

In considering the wasting of bone, we may distinguish simple atrophy from processes where active resorption is concerned. True atrophy, which may be local or general, may be evidenced by diminution of the external size of the bone, by widening of the medullary cavity, or by enlargement of the cancellous spaces. Usually the two last changes are most marked and the bone, as a whole, becomes lighter in weight. Atrophy due chiefly to diminution of formative activity, is seen in old age—*senile atrophy.* The bones become more porous and are more easily fractured, whilst the process of repair tends to be defective and delayed ; the configuration of bones also may become altered in old age. *Atrophy from disuse* is of common occurrence. It is seen when a limb is kept at rest or not actively used, for example, in chronic suppurative disease of bone, in joint disease, etc. As has already been stated, the normal contraction and pressure by muscular action are necessary for the maintenance of the size of a bone, and when these are absent the normal process of building up becomes deficient. *Neuropathic atrophy* is well illustrated in the case of bone. As a sequel of infantile paralysis, the bones of the affected limb become thin and light (Fig. 84). This may in part be the result of disuse, but there seems to be little doubt that it is largely a trophic effect. So also in chronic nervous diseases, for example, locomotor ataxia and syringomyelia, atrophy of bone, due chiefly to enlargement of the cancellous spaces often occurs and may lead to spontaneous fracture. In certain blood diseases, notably in pernicious anæmia and leukæmia, the increase of the marrow leads to enlargement of the medullary cavity and cancellous spaces. The trabeculæ become softened and waste away, but there is no evidence that any special cellular agency is concerned. Examples of local *atrophy due to pressure* are common, but this is as a rule the result of active resorption, usually by osteoclasts.

In certain cases bone undergoes softening, the osseous tissue being replaced by *osteoid tissue,* i.e. osseous tissue with lime-free matrix. The osteoid tissue often covers trabeculæ of surviving osseous tissue. This change occurs in marked degree in rickets and osteomalacia and leads to yielding of the bones. It has long been supposed by many that the change represents decalcification or an active resorption of the lime salts from the surface of the trabeculæ, and the term *halisteresis* has been applied to indicate the change. This, however, has not been proved and it would appear that the appearances may be explained on the view that the osteoid tissue represents the new bone which is constantly being formed but which has failed to become calcified.

Osteoporosis, on the other hand, means a rarefaction of the bone—enlargement of the cancellous spaces with thinning of the trabeculæ, though the latter may be unaltered as regards lime salts. The rarefaction is usually due to active resorptive processes, of which two types are recognised. The one results from the action of multi-nucleated osteoclasts which soften and absorb the osseous matrix, and lead to pits or depressions in which they lie—the so-called *lacunar resorption.* In the other type the bone is absorbed by the ingrowth of capillaries and cells from the periosteum or endosteum or from granulation tissue—resorption by means of *perforating canals.*

HYPERTROPHY

Overgrowth or increased formation of bone is brought about in a great many ways, and the term ‘ hypertrophy ’ has been applied in a somewhat loose manner. The examples of true functional or compensatory hypertrophy form only a small proportion of the cases of bony overgrowth. It is exemplified normally in the increased prominence of ridges at the attachment of muscles when muscularity is specially developed. In a corresponding way in pathological conditions a bone may enlarge when special strain is put on it—for example, one bone of the forearm or leg when the other is rendered useless by ununited fracture or otherwise. But in the great majority of cases, the overgrowth is due to other causes, the two chief of which are (*a*) *chronic irritation* leading to formative osteitis, and (*b*) certain *nutritional disturbances,* sometimes of obscure origin. Examples of the former are the overgrowth of bone in relation to syphilitic lesions, chronic suppuration, and occasionally also tuberculous lesions when the destructive process is in abeyance. Between chronic inflammatory and reparative overgrowth it is often, however, hardly possible to draw a line. The result in either case is, as has been said, comparable to the growth of fibrous tissue which occurs in the soft parts in like conditions. Of the nutritional disturbances causing overgrowth acromegaly is a good example. Here the overgrowth is the result of hyperpituitarism—excessive activity of the anterior lobe of the pituitary—and in this disease there occur superficial thickenings and irregularities of bone, and also enlargement of a bone as a whole, e.g. of the lower jaw. In osteitis fibrosa (p. 833) there may be considerable overgrowth of bone, though this is of osteoid type; in this instance the cause is parathyroid hyperfunction.

Repair of Fracture

The process of repair of bone proceeds on the same lines as in the case of the soft tissues; if we substitute osteoid and osseous matrix for collagenous fibrils, the analogy will be seen to be very close. In both kinds of tissue, the activity of the cells concerned is directed in the first place to occupying the breach of continuity, and thus an abundant new formation of cellular tissue is seen. Then follows the formation of matrix, and the gradual acquisition of the characters of the adult tissue. In the case of bone, not only has the breach to be filled up, but it is manifestly desirable that the necessary support should be got as quickly as possible, and this end is attained by the formation of a large amount of spongy bone. Once the bony support has been supplied, there follows a process of considerable duration in which the bone formed in excess is gradually absorbed, while, at the same time, condensation of the bone forming the union occurs, and the Haversian systems with their lamellæ are arranged so as best to give the necessary support according to the strain put on the bone; thus permanent union is attained.

Structural Changes. When a bone undergoes a simple fracture there is necessarily tearing of blood vessels and of the soft tissues, and a varying amount of hæmorrhage occurs between the broken ends. The periosteum is usually torn through and separated from the bone to a varying extent in the neighbourhood of the breach. Bleeding soon comes to an end and coagulation of the effused blood in great part occurs. Soon there follows a reaction on the part of the vessels. There is exudation from them which leads to a swelling of the tissues at the site; emigration of leucocytes also occurs, these cells wandering into the blood clot and aiding its absorption. Such phenomena are, however, of comparatively short duration and soon pass off in a simple aseptic fracture kept at rest. The process of healing begins by proliferation of cells and new formation of blood vessels. The proliferation takes place in cells of the endosteum and of the deep or cambium layer of the periosteum, as well as in cells derived from the bone, especially from the Haversian canals which, in the region of the fracture, become somewhat widened by absorption of the bone. All these cells possess osteogenic function, that is, are osteoblasts. The new blood vessels accompanied by the cells grow out from the pre-existing blood vessels and make their way into the clot, which gradually becomes replaced by a cellular and vascular tissue.

Where it is in contact with the fracture a certain amount of resorption of bone occurs, as can be seen in radiograms.

In this newly formed tissue the young bone cells are seen to have branching processes from which delicate fibrils pass in all directions. In the process of bone formation the fibrils are seen to become enclosed in a somewhat homogeneous matrix, in which the young bone cells or osteoblasts also become embedded (Fig. 502). Thus osteoid tissue is formed, and this becomes osseous or bony tissue by deposit of lime salts in it. The process occurs in a reticular manner or in trabeculæ, around which the various transitional stages described can be seen. Such a mode of ossification is sometimes spoken of as 'metaplastic,' though the term does not seem to us a suitable one. It is seen also in various other pathological stages where new formation of bone is rapidly going on. The newly formed bone, which has a somewhat spongy character, comes to enclose and unite the ends of the fractured bone, and is known as the 'provisional callus.'

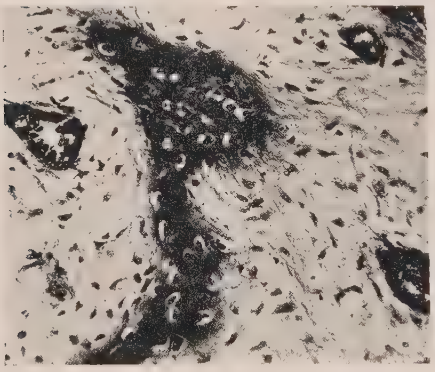

Fig. 502.—Trabecular Formation of Bone, showing transition between cellular tissue with branching cells and bone trabeculæ. × 200.

This callus is sometimes artificially divided into an *internal* callus in the medullary cavity, an *intermediate* callus between the ends of the bone, and an *external* callus outside. The amount of callus varies very much in different cases, and is least abundant in the case of clean fractures, where there is satisfactory apposition and the parts are kept well at rest. On the other hand, when there is movement or when there has been splintering of the bone, callus in excess is apt to be produced. Whilst the newly formed tissue is mainly a vascular osteoid and osseous tissue, islets of young cartilage also may occur in it. This is often a prominent feature in the lower animals and occurs in the human subject, especially when there is a considerable degree of movement. The provisional callus is formed comparatively rapidly and its object apparently is to bring about union as soon as possible. The next stage is one of strengthening the union and adapting the configuration of the bone according to the functional requirements. Parts of the callus are penetrated and resorbed by new blood vessels surrounded by osteoblasts, and these cells then lay down bone by lamellar apposition in the form of Haversian systems (Fig. 504). This process goes on until a more compact type of bone is produced, which forms the permanent union—this is known as the *definitive callus.* At the same time, the external callus is to a great extent absorbed, so that if there has been proper apposition, the configuration of the bone is largely restored. When the bone has united in a bad position, the newly formed bone is not only more abundant but is arranged and moulded in a striking way, according to the muscular requirements (Fig. 503).

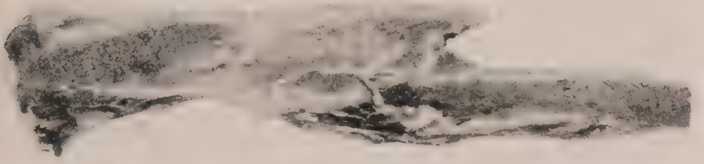

Fig. 503.—Malunited Fracture of Clavicle. × $\frac{3}{4}$.

In the case of a *compound fracture*, repair proceeds in a similar manner, but the entrance of organisms may cause suppuration in places, which interferes with the formation of callus and may lead also to the resorption of callus already formed. When there is exit for the pus the healing takes place very much as in a granulating wound; there is an advancing line of ordinary granulation tissue behind which bone formation goes on, and ultimately any spaces occupied by pus may be obliterated and the process of bone formation may be completed. Just as in the soft tissues where there is long continued suppuration, much overgrowth of fibrous tissue occurs, so in the case of compound fracture there may be considerable and irregular formation of new bone. When a portion of dead bone is present, it becomes a nidus for organismal growth, and pus forms around it; and suppuration may, in this way, be kept up for an indefinite period of time, the pus being discharged from the sinus which leads down to the dead bone.

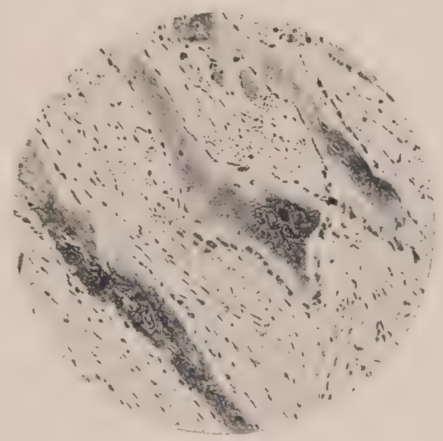

Fig. 504.—Process of Lamellar Ossification.

Note the layer of osteoblasts surrounding the newly formed trabeculæ. × 60.

Transplantation of Bone. This procedure is employed to restore gaps in bone, caused by fracture or necrosis, and for other purposes. The bone is ordinarily used in the living state as a single transplant or as small fragments; it is usually taken from the patient

—*autoplastic* transplant. The dead bone of animals is, however, sometimes used. Very successful results are obtained by transplantation, but the bone acts mainly as a scaffolding on which new bone may be formed and probably also by stimulating ossification. That mere presence of bone may act in the latter way is indicated by the occurrence of ossification in connection with calcareous deposits in the soft tissues. Even in the case of living autoplastic grafts, only the cells in the superficial parts of the bone can derive nourishment from the tissue fluids and survive. The rest of the bone dies ; it is largely resorbed or portions may become incorporated with the living bone as an inert substance. The preservation of the periosteum is believed to be of importance as it contains osteoblasts which may participate in the formation of new bone.

INFLAMMATORY CHANGES

Different terms are applied to inflammations of bone according to the site—periostitis, osteitis proper, and osteomyelitis—but these should not be taken as necessarily indicating separate affections ; one may lead to another, and sometimes all three are present together. If a bone as a whole during the period of growth is considered, it will be seen that, with the exception of the parts in relation to cartilage, it consists of fully formed osseous tissue enclosed everywhere by a cellular osteogenic layer—the tissue along the Haversian canals, the periosteum, and the endosteum between the bone and the marrow. In the adult this layer, though comparatively inactive and less in evidence, is still potentially present. Pyogenic organisms carried by the blood stream may settle in any part of this tissue and thence spread to other parts, and such infection occurs most frequently in the earlier years of life before ossification has been completed.

Acute Osteomyelitis.[1] This is a relatively common affection and one of great importance on account of the serious results which are produced by it. Its occurrence is definitely related to the period of active growth of bone, and is commonest between the ages of 8 and 12 ; boys are more frequently affected than girls. It has been shown experimentally that the bones of young animals are most susceptible to infection when staphylococci are injected into the blood. In the human subject the bones most frequently affected are the long bones of the leg and arm, especially the femur and tibia, though other bones such as the clavicle, scapula, ribs, and occasionally a phalanx, vertebra or pelvic bone, may be the seat of the disease. Sometimes multiple lesions occur. Whilst suppurative osteomyelitis may be produced by various pyogenic organisms, by far the commonest cause is the *Staphylococcus aureus*, and especially is this the case in the severest types of the disease. The *Pneumococcus* comes next in order of frequency, whilst the other pyogenic organisms are relatively uncommon as causal agents. There may be an inflammatory or suppurative lesion elsewhere from which the organisms are carried to the bone, but not infrequently the path of entry cannot be traced and is probably some slight lesion of the skin or a mucous membrane.

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[1] For details on this and other surgical affections, see *A Text-book of Surgical Pathology*, by C. F. W. Illingworth and B. M. Dick, 4th edit., London, 1941.

STRUCTURAL CHANGES. In most cases, the primary seat is in some spongy part of the bone, usually towards the end of the diaphysis, i.e. in the metaphysis, and from this both medullary cavity and periosteum may become involved. When the organisms reach the medullary cavity of a long bone the suppuration often spreads widely, so that the cavity becomes largely occupied by pus. At the epiphyseal line, when ossification is going on in a young subject, extension of the pus occurs more readily in a transverse direction than onwards into the epiphysis on account of the avascular nature of the epiphyseal plate. The infection reaches the periosteum in this way or by the Haversian canals and spreads along the shaft, as the attachment of the periosteum at the epiphysis usually prevents its travelling over the latter. Ultimately, a large part or even the whole of the diaphysis becomes denuded of its periosteum and is bathed in pus. The pus may burst through the periosteum and lead to diffuse suppuration in the muscles and other soft tissues, and later, if the condition be not treated, may come to discharge externally. Occasionally a joint may become secondarily involved and suppurative arthritis may be set up.

The suppurative changes described have an important effect in leading to *necrosis* of bone. Suppurative periostitis by itself leads to necrosis of only a superficial layer of bone, owing to the anastomoses with the vessels coming from the interior of the bone; whilst in the case of suppurative osteomyelitis also, the resulting necrosis, though varying in degree according to the amount of vascular involvement, may be limited to the neighbourhood of the suppuration. If, however, both lesions are extensive at the same time, the corresponding bone is completely deprived of its blood supply and undergoes necrosis. Especially will this be the case when, as may happen with a large accumulation of pus under the periosteum, the nutrient artery becomes involved and thrombosis occurs in it. In extreme cases, death of the whole diaphysis may result, and then the dead bone becomes separated from the epiphyses and forms a large sequestrum (Fig. 505). At certain parts, especially towards the ends, the dead bone may become eroded by granulation tissue, and irregular absorption thus results; but the part actually bathed in pus undergoes little change and thus the surface of the dead bone may remain smooth for a long time. As the process becomes less acute, new bone is usually produced under the periosteum and this may form an encasing sheath to the dead bone, known as a 'new case' or 'involucrum.' This new bone is somewhat irregular and is often perforated by openings or *cloacæ* by which the pus beneath communicates with pus outside or with a discharging sinus. Nowadays, because of the prompt operative interference usually carried out, these changes are not often met with, but in previous times, extensive new formation of bone was not uncommon (Fig. 506).

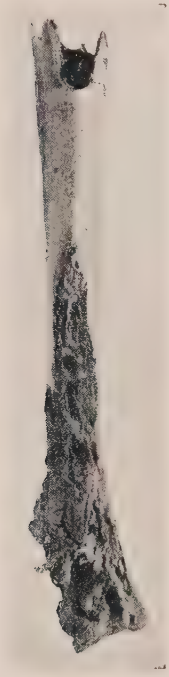

FIG. 505. — Sequestrum of Shaft of Tibia from a case of acute Suppurative Osteomyelitis.

Note the partial absorption of the bone at its ends.

We have described the disease in its severer forms, but suppuration may sometimes implicate only a part of the medullary cavity, and then great thickening of bone occurs around it; the medullary cavity above and below it may be closed by reactive formation of bone. The term 'Brodie's abscess' is applied by surgeons to a local abscess of chronic nature usually situated in the metaphysis of a long bone. It is as a rule surrounded by dense bone and may give rise to external swelling. The contents of the space may be pus, but in very chronic cases are often a clear fluid which may be sterile. The condition apparently represents a localised pyogenic affection of the bone which has undergone healing.

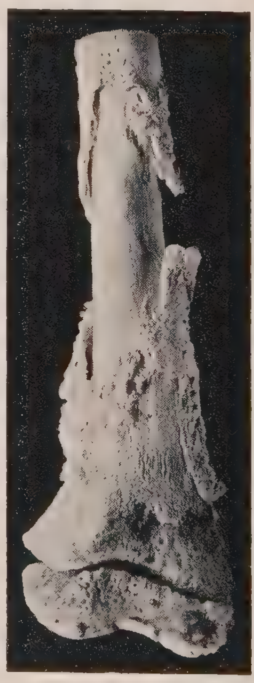

FIG. 506.—Femur from a case of long-standing suppurative Osteomyelitis and Periostitis, showing the irregular formation of new bone round the sequestrum.

COMPLICATIONS. In addition to the severe lesions in the bones produced by suppurative periostitis and osteomyelitis, these affections may lead to a very grave general infection. This is especially the case in osteomyelitis due to staphylococci, where, owing to the delicate character of the vascular channels in the marrow, the organisms readily invade the blood and may produce an ulcerative endocarditis, abscesses in the lungs, kidneys, myocardium, etc., and these secondary lesions may take place when the affection of bone is not extensive or is at an early stage. The causal organisms are present in the blood and may be obtained from it by culture.

Secondary abscesses are less frequent in the case of infections with other bacteria, though multiple septic arthritis may follow when streptococci are present. In former days amyloid disease was not infrequent as a result of the long-continued suppuration with sinuses which often followed, but fortunately this is now of relatively rare occurrence.

The account given concerns the disease in its commonest and most severe type, ordinarily due to the *Staphylococcus aureus*, but milder types are met with. Pneumococcal infection is the commonest of these and is met with especially in infants and young children. Fraser found it in 18 per cent. of all cases of osteomyelitis. The exudate may not pass beyond the stage of being a turbid serum, and resolution may occur. Sometimes, however, suppuration follows.

FIG. 507.—Chronic Suppurative Osteomyelitis of Femur.

The lower part of the medullary cavity contains pus and granulation tissue; there is sclerosis of bone around and the medullary cavity above is obliterated. Opening on right is operational.

Acute Periostitis. What is often called acute periostitis may occur as the result of traumatism, the condition being then of the nature of inflammatory œdema with swelling, with little accompanying leucocytic infiltration. Apart from this, it is produced by bacterial invasion and often assumes a suppurative character. It may result from an external wound or from the extension of organisms from an ulcer, or, in the case of the jaws, from a carious tooth. In most cases, however, and in those of severest form, the infection is by means of the blood stream, and organisms of various kinds may be concerned. Undoubtedly, the gravest form is that produced by staphylococci, and especially by the *Staphylococcus aureus*, and this is usually associated with and secondary to osteomyelitis, as has been described above. Suppurative periostitis may, however, be produced by streptococci, by pneumococci, *B. coli* and *B. typhosus*. The last mentioned occasionally produces successive periosteal inflammations, especially of the ribs, a considerable time after an attack of typhoid. If periostitis is attended by much suppuration, the pus may burst through the periosteum and lead to suppuration in the tissues outside; whilst in slight cases the pus may become encapsulated and inspissated and this may be attended by some thickening of the bone.

A form of suppurative affection of bone with necrosis sometimes occurs amongst workers exposed to the action of the fumes of phosphorus—hence known as *phosphorus necrosis*. The lower jaw is usually the seat of the disease, though the upper jaw is sometimes involved. The action of the phosphorus is favoured by the presence of any local lesion such as a carious tooth, and the pathological changes are usually of very chronic character. At first there is a chronic periostitis and osteitis as the result of the irritation, and new formation of bone occurs on the surface; in this way the affected bone becomes irregularly thickened. The most serious effects occur later, and are the result of invasion by pyogenic organisms which lead to suppuration underneath the periosteum. The suppurative process then tends to spread, and ultimately a large proportion of the jaw may undergo necrosis. As in other cases of necrosis, new formation of bone may take place underneath the periosteum, and when the sequestrum is separated or surgically removed, a considerable amount of restoration of bone may follow.

SPECIFIC INFLAMMATIONS

Tuberculosis of Bones. In considering this subject it will be convenient also to deal with the disease as met with in joints, the lesions in the two situations being so often associated. In the great majority of cases tuberculosis of bones is hæmatogenous; that is, it is the result of a few bacilli being carried by the blood stream from tuberculous lesions elsewhere, for example. in lymphatic glands, lungs, etc. Less frequently, it results from lymphatic spread from a tuberculous lesion in the vicinity, sometimes from a tuberculous joint. The disease usually starts in the spongy bone, and is oftenest met with in the small bones of the hands and feet, vertebræ, spongy parts of the long bones of the limbs, especially in the metaphyses and epiphyses. Affection of the bones of the cranial vault is relatively uncommon—a contrast to what is seen in syphilis; but the disease is not so rare at the base of the skull, e.g. in the petrous, body of the sphenoid, etc. No bone, however, can be said to be entirely exempt. In childhood the vertebral column and the bones of the lower limbs are the commonest sites; affection of the bones of the upper limbs becomes more frequent as age advances. Primary lesions do not often occur in connection with the periosteum—here also there is a contrast to syphilis; they are sometimes met with in the ribs and bones of the face, but chiefly as the result of spread from adjacent disease. Bones may be affected by tuberculosis at any period of life, but its occurrence is commonest in childhood and early life; in children, it is in most cases secondary to tuberculosis of lymphatic glands or a pulmonary lesion can be found. In a considerable number of cases the origin of the disease, both in bones and joints, has a relation to injury, and it has been shown experimentally that when the bacilli have been introduced into the blood stream, trauma favours their settling at the site, and producing a lesion. It has been suggested by some that injury may be the means of waking up a dormant tuberculous lesion, and this also has to be regarded as a possibility, especially in view of the fact that tubercles not infrequently undergo a process of healing.

The part played by the two types of tubercle bacilli in bone and joint tuberculosis varies greatly in different places. As a rule, the human type is present in the vast majority of cases, but in Scotland about 35 per cent. of the cases have been due to the bovine type.

Structural Changes. When tubercle bacilli have settled in the marrow of spongy bone they give rise to the usual result, namely, the formation of tubercles. This primary lesion then extends and may assume one of two main types, though intermediate conditions are met with. On the one hand, there may be little or no caseation, and much soft granulation tissue may be formed, of structure similar to that seen in the synovial membrane of joints—what is sometimes called 'tuberculous fungus.' Its growth is attended by absorption of bone or *caries* (Fig. 508), and sometimes the bone in the vicinity not yet invaded may become more porous owing to atrophy of the trabeculæ. On the other hand, the lesion may assume a caseating type, the newly formed tissue undergoing caseous necrosis, while the partly absorbed bone trabeculæ become broken up and mixed with the caseous material; this is well exemplified in the case of the vertebræ. Again, portions of bone may become surrounded by the caseous change and undergo necrosis before they have been absorbed, and thus sequestra are formed—the condition being known as *carionecrosis*. Occasionally necrosis may occur in infarction-like areas by interference with the arterial blood supply. This is specially seen in the epiphyses, where the base of a wedge-shaped necrotic area is at the surface of the bone under the cartilage; in this way the disease may extend to the joint. The cause of such necrosis is probably, in most cases, a tuberculous endarteritis of nature similar to that seen in tuberculous meningitis. By a combination of the conditions mentioned, namely, formation of tuberculous granulation tissue, carious absorption with caseation, and actual necrosis, great destruction of bone is often produced.

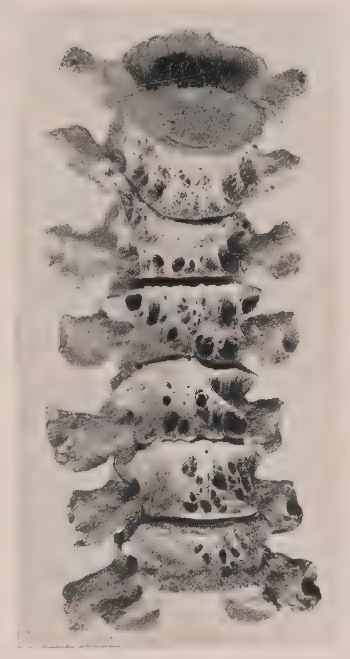

Fig. 508.—Portion of Vertebral Column, showing destructive changes caused by Tuberculous Caries (macerated and dried specimen).

Results. In some cases the tuberculous foci may undergo healing and become surrounded by fibrous tissue or by sclerosed bone.

This is of common occurrence, especially in the early years of life. Overgrowth, however, of bone is relatively little in evidence as compared with what occurs in syphilis. It must be borne in mind, however, that tubercle bacilli may remain in these healed foci for a long time, and thus the disease may become again progressive at a later period. Instead of healing, the disease may go on spreading and affect other structures. It may involve a joint, either by reaching the articular cartilage by direct extension or by involving the periosteum and then the capsule of the joint. When the periosteum becomes affected the caseous material is often invaded by polymorpho-nuclear leucocytes and softened; thus caseous pus may result and by progressive accumulation may form a large collection. This is common in connection with the bodies of the vertebræ, and the pus may penetrate the sheaths of muscles and extend in their substance. In this way when the lower vertebræ are involved a psoas or lumbar abscess may be produced, and when the disease is of the cervical vertebræ, a large collection of pus may form behind the pharynx—retro-pharyngeal abscess. As the substance of the vertebral bodies is involved by the caseous process, they yield or collapse in front, and thus angular curvature of the spinal column results, which is known as *Pott's disease.* Ultimately the spinal cord may become involved and its functions interfered with by a transverse lesion. Occasionally the atlas vertebra is the seat of disease, and its articulation with the occipital bone and also the process of the axis may be involved. Sudden death may result from yielding of the structures and resulting pressure on the upper part of the spinal cord.

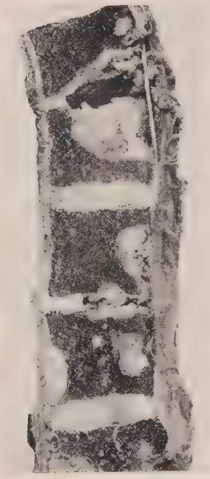

FIG. 509.—Multiple Tuberculous Areas in Bodies of Vertebræ.

Tuberculous lesions of bone are sometimes single, or at least appear to be so, sometimes clearly multiple. For example, several distinct foci may be seen in the vertebral column (Fig. 509), though spread of the disease by the periosteum may lead to successive involvement of a number of vertebræ. In children sometimes a number of bones of the fingers may be involved. The disease occurs in the central parts of the bones, and there is abundant formation of tuberculous granulation tissue which leads to absorption and also expansion of the bone, so that it may be reduced to a mere shell. The term *tuberculous* or *strumous dactylitis* is applied to such a condition. In this condition, as in others, caseous pus may form in the soft tissues outside, and then ulceration through the skin with the formation of sinuses may follow. It should be added that tuberculous lesions in relation to skin or mucous membranes may become secondarily invaded by pyogenic organisms, and thus septic inflammation and suppuration are superadded to the changes of tuberculosis. In extensive tuberculous disease amyloid degeneration may occur in the internal organs.

Tuberculosis of Joints. Tuberculous disease is very common in joints, the great majority of cases occurring in the early years of life. Almost any joint in the body may be affected, but the disease is commonest in the larger joints of the limbs, especially the hip- and knee-joint, though the smaller joints of the tarsus, carpus, etc., are not seldom sites of the disease. In one group of cases there is a previous lesion in an adjacent epiphysis, and from this there may be direct spread to the under surface of the cartilage, or the extension may be by way of the periosteum. It is now generally accepted that secondary extension from the bone is much the more frequent occurrence. It is specially liable to happen when, as in the hip joint, the capsule extends beyond the epiphyseal line. When a joint becomes infected by either route, there occurs an extensive formation of tubercles in the synovial membrane, and these are accompanied by an abundant growth of soft gelatinous granulation tissue; this comes to line the capsule and gradually encroaches on, and produces absorption of, the articular cartilages (Fig. 511). At an early stage the tissue growing over the cartilage may form a thin vascular membrane in which tubercles may be visible (Fig. 510). When the granulation tissue is fully formed it has often a brownish-pink and gelatinous appearance, and while tubercles may be visible to the naked eye, there is often nothing to indicate its tuberculous nature; sometimes, however, it is studded with caseous patches. Microscopic examination shows a very abundant vascular granulation tissue in which numerous giant-cell systems are present, and not in-

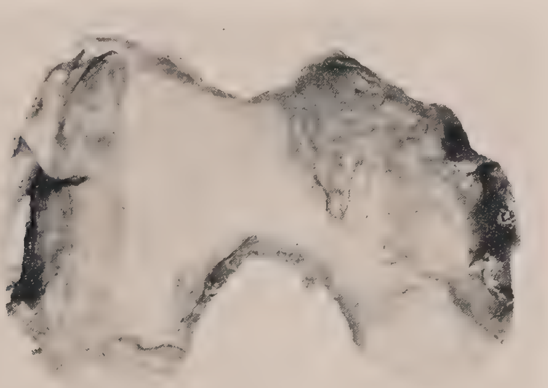

FIG. 510.—Early Tuberculous Disease of Knee-joint.

Note the spread of vascular tissue with tubercles over the surface of the cartilage.

frequently little caseous change is seen ; tubercle bacilli are very scanty as a rule. There is usually a certain amount of effusion into the joint, at first clear but later turbid or even purulent, the pus containing a considerable amount of granular débris in addition to degenerated polymorpho-nuclear leucocytes. These changes are attended by swelling, usually painless and without signs of acute inflammation —hence the term 'white swelling.' Not infrequently there are numerous loose bodies like grains of rice or melon seeds, which have a dense structureless appearance. On microscopic examination some are found to be fragments of granulation tissue which has undergone necrosis or fibrinoid degeneration, whilst others are simply condensed masses of fibrin. The ligamentous structures become invaded by the tuberculous tissue, swollen and softened ; thus abnormal lateral movement of a joint frequently results. Destruction of cartilage also occurs, partly by absorption, as already described, and partly by actual necrosis when the disease reaches it from the underlying bones. The destruction of cartilage is usually followed by extensive

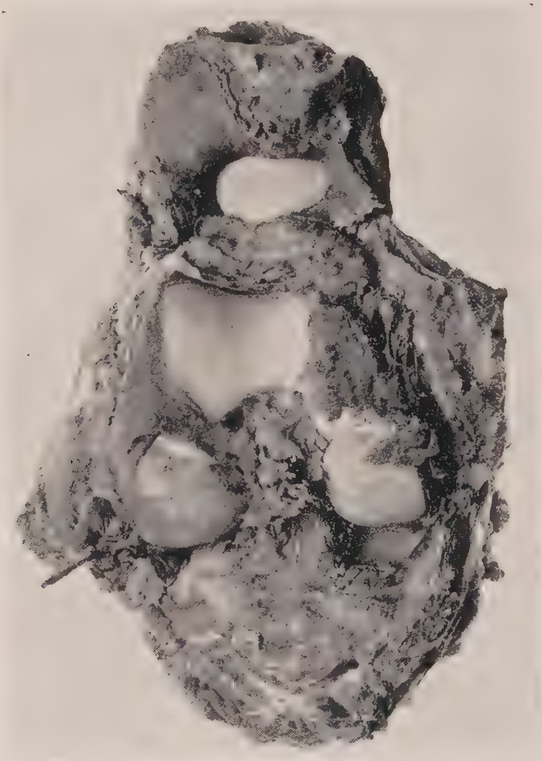

FIG. 511.—Tuberculous Disease of Knee-joint, showing extensive growth of Tuberculous Granulation Tissue over articular Cartilage and destruction of it. There is much growth around the patella seen in upper part of figure.

caries of bone with much resorption; this is often a prominent feature in the hip-joint, for example, where the articular end of the femur may be extensively eroded. There may be formation of caseous foci with suppurative softening in the capsule of the joint and in the soft tissues outside, and from the latter situation the pus may break through the skin surface and give rise to sinuses. Ultimately the affected joint may become completely disorganised. In favourable cases, and especially when the joint is immobilised, the destructive changes may be arrested, and there then follows absorption of the tuberculous tissue, with growth of fibrous tissue; and in this way the joint becomes fixed in greater or less degree. Even where there is considerable caries of the bone, healing may follow. Osteophytic growths form at the eroded margins, and by their union osseous ankylosis may follow.

The above description applies to the disease as commonly met with in a large joint, but the changes in the smaller joints are of corresponding nature. Sometimes, however, the disease is of a very chronic nature, and the changes are more of an atrophic type, attended with gradual erosion of the cartilage and new formation of bone at the margins. This condition is called 'tuberculosis sicca,' and it may simulate osteo-arthritis in its characters. It occurs in the later years of life, and the shoulder-joint is the commonest site of the affection.

Tuberculous Tenosynovitis. Tuberculosis may also affect the tendon sheaths, especially the flexor sheath of the wrist, and the changes resulting resemble those in joints. There may be great effusion of fluid into the sheath and 'melon seed' bodies may form in the fluid, or there may be extensive growth of fungous granulation tissue in the interior of the sheaths.

Syphilis of Bones. Affections of the osseous system are common in the tertiary stage of syphilis. As compared with tuberculous disease, formative processes are more in evidence, and accordingly there is more irregular production of bone as the result. Another point of difference is that the lesions most commonly originate in the periosteum, whereas in tuberculosis this site is comparatively rare. The bones affected in syphilis are chiefly the long bones (especially the tibia), the flat bones of the skull, the sternum and the clavicle; the palate and nasal bones also are not infrequently involved. As regards the characters of the lesions, they correspond with those in internal organs, that is, they are partly of the nature of chronic inflammation with induration (sclerosis), and partly gummatous with destruction of tissue. Evidence of periosteal affection occurs even in the secondary stage; there may be somewhat painful areas of swelling, especially over the tibia and bones of the skull, and some thickening of bone may follow. Usually, however, such lesions are of a transient type. In the tertiary stage the formation of distinct gummata, which present the usual characters, is of common occurrence in the periosteum;

the centre may undergo necrotic softening and the lesions may become adherent to the skin, ulcerate and discharge. Secondary infection with pyogenic organisms follows and the destructive changes are increased. The bone underneath the gumma may undergo caries and resorption, a depression with rough floor thus resulting, while at the periphery there is considerable formation of bone, and a raised and irregular bony margin results. The periostitis is often associated with osteitis; great thickening and sclerosis of the bone may occur and the medullary cavity may be encroached upon. The lesions may be multiple and widespread over a bone, e.g. the tibia or clavicle; the bone is often enlarged as a whole, whilst the surface is extremely irregular, there being pits or depressions with nodules and ridges between (Fig. 512). Another result is actual necrosis with formation of sequestra; this is common when the lesions are extensive, so that the vascular supply of parts becomes interfered with. Such an occurrence is well exemplified in the case of the skull, where considerable areas of bone may die and sequestra become separated; gummata form both outside and inside the skull, and by a combination of the destructive and formative processes, the appearance comes to be of a striking nature. The bone is thickened and its surface presents depressions and nodules, and, it may be, also apertures (Fig. 513). Such lesions are met with

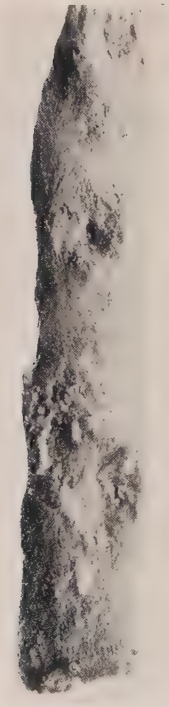

FIG. 512. — Syphilitic Disease of Periosteum of Tibia, showing nodular thickenings and eroded areas in the bone.

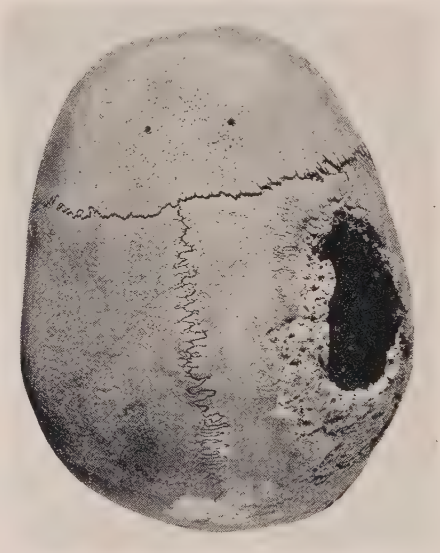

FIG. 513.—Syphilitic Disease of Skull.

Note the large aperture with irregular margins resulting from a gumma.

only in very severe forms of untreated syphilis and are rarely seen nowadays, but examples are to be found in most museums.

In the case of the palate and nasal bones, gummatous periostitis may be followed by superficial ulceration, and then the ulcer may perforate deeply and lead to necrosis of bone ; pyogenic organisms, of course, become superadded. The gumma at the extremity of a bone occasionally extends to a joint and gives rise to a gummatous arthritis. Gummatous foci may form also in the bone marrow, but this is a relatively rare occurrence.

Lesions of the bones are common in *congenital syphilis* ; the commonest effect is seen at the epiphyseal lines, especially in the long bones, and is known as syphilitic *osteochondritis*. The lesion is usually present at birth, and often becomes less marked afterwards. Instead of the thin and well-defined line of ossification, there is a broader band of a yellowish appearance with slightly irregular margins (Fig. 514 C). Sometimes gritty calcareous material may be detected in it, and evidence of softening may be seen. The ultimate result may be separation of the epiphysis, either spontaneously or as the result of slight trauma. Microscopic examination shows that the zone of proliferation of cartilage cells has increased, the cells undergoing an excessive and somewhat irregular proliferation which leads to great thinning of the matrix. The lines of proliferated cells are usually, however, comparatively regular (Fig. 515). In the thinned matrix lime salts

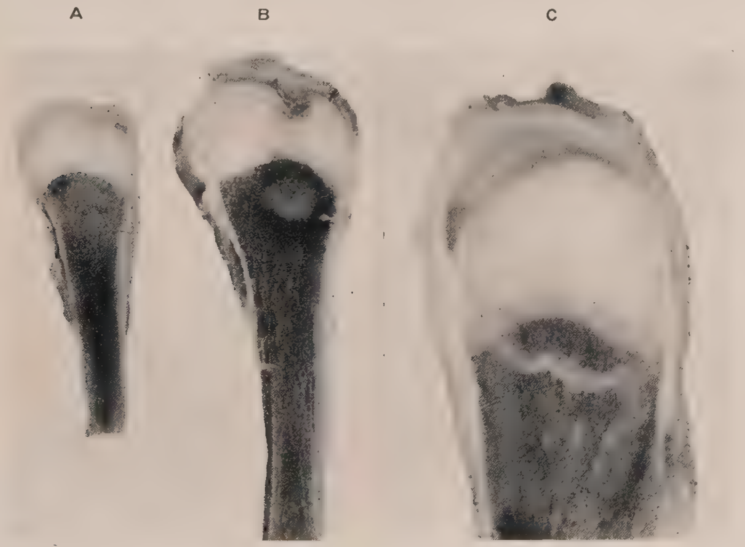

Fig. 514.—Lesions of Bones in Congenital Syphilis.

A and B show gummatous epiphysitis (natural size), and C the irregularity of the epiphyseal line at a less advanced stage. (J. W. S. B.) (× 2).

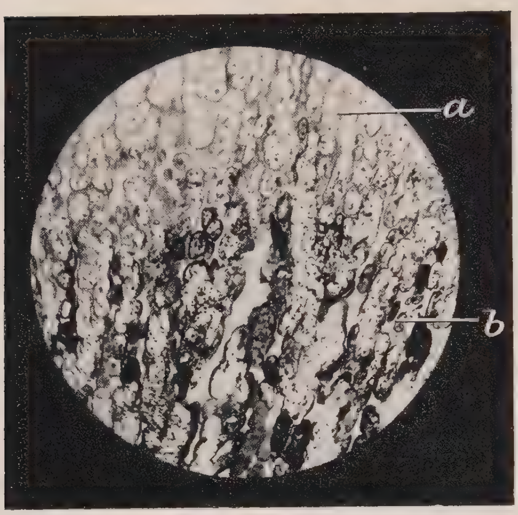

Fig. 515.—Syphilitic Epiphysitis or Osteochondritis.
a, cartilage; *b*, zone of calcified trabeculæ with cellular tissue between. × 60.

become irregularly deposited, a sort of calcified trellis-work resulting; bone formation is interfered with, and any bone trabeculæ formed are small and irregular. When such a stage has been reached the delicate calcified trabeculæ are easily broken across, and this occurs at some distance down in the area of proliferation. In other cases, there is more abundant formation of cellular granulation tissue, which undergoes degeneration and softening. This change, which is gummatous in nature, usually starts in the centre and spreads to the periphery, separation being again the result (Fig. 514 A, B).

The other common lesion in congenital syphilis is periostitis, especially of the long bones, which may be followed by considerable new formation of bone. This often occurs when the osteochondritis is healing. Occasionally a bone may be affected almost in its whole extent and come to be somewhat spindle-shaped (Fig. 516). As in

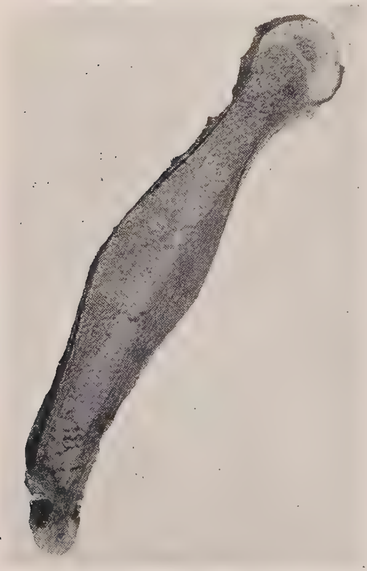

Fig. 516.—Humerus from a case of Congenital Syphilis, showing great sub-periosteal thickening which gives the bone a spindle form.

the adult, softening of a gummatous mass may take place, and ulceration through the skin may follow. Another manifestation of the disease is known as *syphilitic dactylitis*, which affects the bones of the hand, more rarely those of the foot. Sometimes the phalanges and metacarpal bones of several fingers are affected. The lesion, which may start from the epiphyseal line or from the periosteum, leads to redness and swelling of the part, and occasionally discharge of necrotic material may occur through the skin. A similar change is not uncommon in the periosteum of the nasal septum. Here destruction of bone, often attended by perforation, leads to falling in of the bridge of the nose, a change which is frequent in congenital syphilis.

Syphilis of Joints. In contrast to tuberculosis, syphilis comparatively seldom gives rise to important lesions of joints. In the secondary stage, effusion occasionally takes place into a joint ; the sternoclavicular is said to be the commonest site. In tertiary syphilis, the usual changes which affect the soft tissues, namely, gumma and chronic interstitial inflammation, may occur in the capsule of a joint, leading to swelling and thickening of its tissues ; stiffness and restriction of movement result, and there may be sometimes erosion of cartilage. Occasionally a joint may become affected from a gumma of an adjacent part of the bone, and chronic arthritis is thus set up. In the congenital form, synovitis with effusion is not infrequently secondary to syphilitic epiphysitis, it may be with separation of the epiphysis, and swelling of the joint is usually a prominent feature. Such an affection is not uncommon in the knee-joint. Actual gumma in the capsule is said to occur, but this is very rare. It is to be noted that the bone and joint lesions in congenital syphilis may resemble those of tuberculosis and may be mistaken for them.

Actinomycosis. In this disease the bones may become affected secondarily by extension from the suppuration in the soft tissues. This is met with chiefly when the primary lesion has been in the region of the mouth, the upper or lower jaw then becoming involved ; or in the region of the pharynx, when extension to the vertebral column is not infrequent. The lesion is essentially one of caries with pus formation ; and as it is progressive in character, there is little or no new formation of bone. In an advanced case the bodies of the vertebræ may be extensively eaten away. Occasionally the pelvis becomes secondarily involved when the disease is in the lower part of the abdomen. In the ox, on the other hand, the lesions are of less destructive kind, and while parts of the bone are destroyed there may be new formation of bone at the margin ; this is well seen sometimes in the lower jaw, the bone becoming excavated centrally whilst new bone is formed peripherally. It may be added that in Madura disease, which is caused by an allied streptothrix, the prominent feature is extensive carious destruction of the bones of the foot.

DISTURBANCES OF NUTRITION AND GROWTH

Under this heading will be considered a somewhat heterogeneous group of more or less chronic conditions, which have only this in common, namely, that they are not produced by micro-organismal invasion and accordingly cannot be classed amongst the infections. Some lesions of this class result from diet deficiencies, others from disease of endocrine glands, whilst in others, again, the causation is unknown. In some instances the disease is acquired after birth, in others it is of congenital origin. In the latter case there may be a deficiency in endochondral ossification—*achondroplasia*, or the defect may be in bone formation generally—*osteogenesis imperfecta*. *Malacia* or softness of bone is often a marked feature in the acquired affections, notably in rickets, osteomalacia, and osteitis fibrosa.

Rickets. This affection is characterised by deficiency in the process of ossification and by the formation of much osteoid tissue instead of bone ; softening and yielding of the bones thus result. The proliferative changes preliminary to ossification are in excess, but the process is not carried to its normal completion. Whilst in mild cases the changes may be confined to certain bones, yet rickets is to be regarded as a general disease, and in some cases the whole skeleton may be profoundly affected. It is essentially a disease of infancy, usually starting in the first or second year of life and is rarely manifest before the end of the first six months. It continues in an active or florid state for a varying period, sometimes for several years, and its passing off is characterised by the completion of ossification and hardening of the bones. Permanent distortion of the bones is of common occurrence, as they become fixed in the form which they acquired when their tissues were soft. There is also a congenital form of rickets but it is of very rare occurrence.

Structural Changes. Naked-eye appearances show disturbances in both endochondral and membranous ossification. At the epiphyseal junction, say of a long bone, instead of there being a sharp line, the zone of ossification is widened out into a broad band of semi-translucent white appearance, irregular, especially next the diaphysis ; this band may show small vascular patches and, where calcification is occurring, yellowish points. The area of ossification is also widened transversely, so that swelling of the bones in the region of the epiphyseal line may be a distinct feature. This swelling is often very marked at the costo-chondral junctions, so that a row of rounded projections is formed at the end of the ribs, to which the term ‘ rickety rosary ’ is applied (Fig. 517). The disturbance of intramembranous ossification is well seen in the case of the cranial bones. The skull becomes less rounded and somewhat box-like in form. The fontanelles are widened and bosses of soft spongy bone are formed over the frontal and parietal bones; and the pericranium, when stripped, takes with it vascular projections and leaves a somewhat eroded appearance. The texture of the bones is sometimes so soft that they can be cut with a knife. Corresponding changes occur in other bones and they become softened and yielding; the long bones tend to bend in various directions and sometimes greenstick fracture occurs. The vertebral column may become curved, sometimes to a marked degree, the chest wall becomes depressed by the yielding of the ribs a short distance behind their anterior ends, and consequently the sternum is pushed forwards —a deformity which is characteristic of rickets. There may be irregular subperiosteal formation of new bone along the ribs and long bones, giving rise to elevations, whilst new bone may be formed also from the endosteum so that the medullary cavity is encroached upon. When the active stage of the disease comes to an end, ossification proceeds and the bones often become abnormally dense and heavy. Some deformities may be lessened or even recovered from, but many become permanent. Thus the long bones are permanently twisted, bow-leg, knock-knee, etc., being common, and they are often markedly shortened, so that a condition of rickety dwarfism results. Spinal curvature of the nature of scoliosis, which may be severe, is a frequent result; the pelvis remains flattened, with diminution of the antero-posterior axis, and in women this change may come to be a serious impediment to parturition.

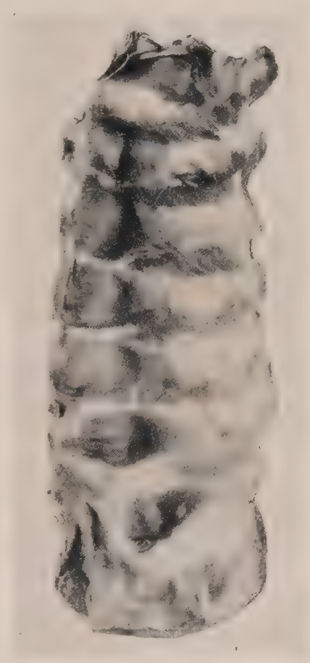
Fig. 517.—Portion of rickety Chest Wall seen from within, showing the Swellings near the extremities of the Ribs.

The changes found on *microscopic examination* may be described in general terms as an increase of the proliferative changes with imperfect ossification; the matrix formed in excess by the osteoblasts, however, does not become calcified and thus osteoid tissue results.

If one examines the process of ossification at the epiphysis, the zone of proliferation of cartilage cells is seen to be much widened (Fig. 519). Next to the cartilaginous extremity the cells are arranged in rows; but lower down, that is, towards the shaft, the linear arrangement becomes irregular and the cells are of larger size. Lime salts may be irregularly deposited in the matrix thinned by the cells, but are scanty in amount. The broad zone of altered cartilage is seen to be permeated in an irregular way by blood vessels surrounded by cells like osteoblasts, and the outermost cells are becoming embedded in the osteoid tissue which they have formed (Fig. 520). This growth of osteoid tissue is quite uneven in distribution, and areas of cartilage are seen between; sometimes islets of cartilage are quite cut off by the advancing osteoid tissue. New blood vessels also may grow in from the perichondrium at this level, and around them osteoid tissue is formed in a similar way. In bones ossified in membrane the Haversian canals become widened; there is an excess of cells under the periosteum and around the vessels, and the trabeculæ are covered, or entirely formed, by osteoid tissue (Fig. 521). When the active stage of the disease passes off, lime salts are deposited in the osteoid tissue and ossification is completed. Thus permanent

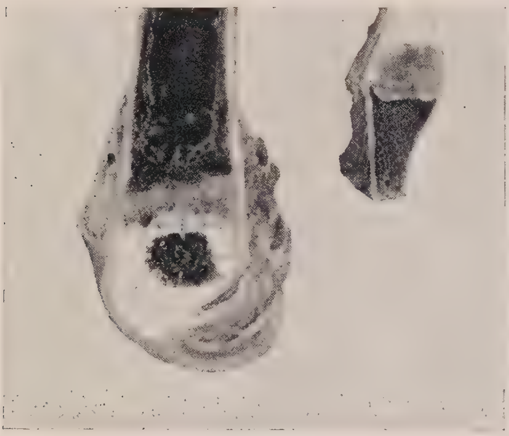

Fig. 518.—Section through Lower End of Femur and Rib at Costo-chondral Junction in Rickets. (Natural size.)

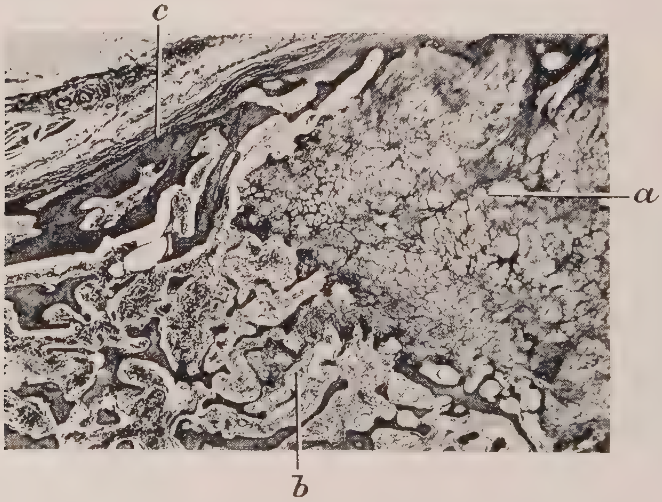

Fig. 519.—Section through Costo-chondral Junction in Rickets.

a, Cartilage with osteoid formation; *b*, spongy bone and osteoid tissue; *c*, periosteum. × 15.

excess of bone, often of dense character, and deformities may result in the sites of the disease.

The structural changes in the skeleton are associated with *alterations in mineral metabolism*. Telfer has found that the most important of these is a diminished absorption from the bowel of lime and phosphoric acid in nearly equal proportion, so that there is a large excess of calcium phosphate in the fæces, and the excretion of phosphorus by the urine is diminished. Normally in the child there is a daily retention of about 0·08—0·1 gm. of CaO per kilo. per day, and about the same amount of P_2O_5. In rickets, in the active stage, the retention may be reduced to 0·02—0·03 gm. The calcium content of the blood, however, is practically normal as a rule; though it becomes reduced in cases where tetany supervenes. The plasma phosphorus is usually reduced. In the healing phase of rickets, the absorption of lime and phosphoric acid from the bowel rises above the normal, and the urinary excretion of the latter likewise becomes increased. Telfer has found also that the administration of cod-liver oil during

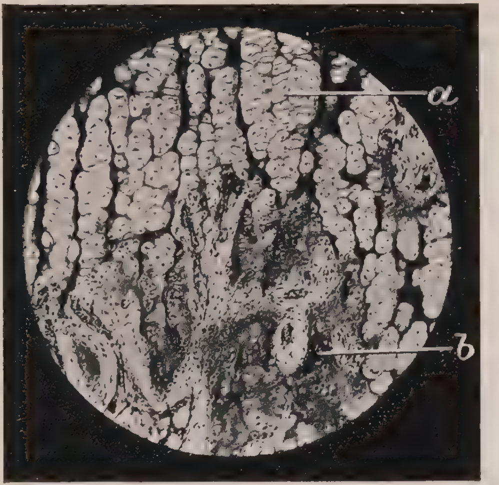

FIG. 520.—Changes at Epiphyseal Line in Rickets.

a, Zone of proliferating cartilage cells; *b*, irregular formation of osteoid tissue. × 60.

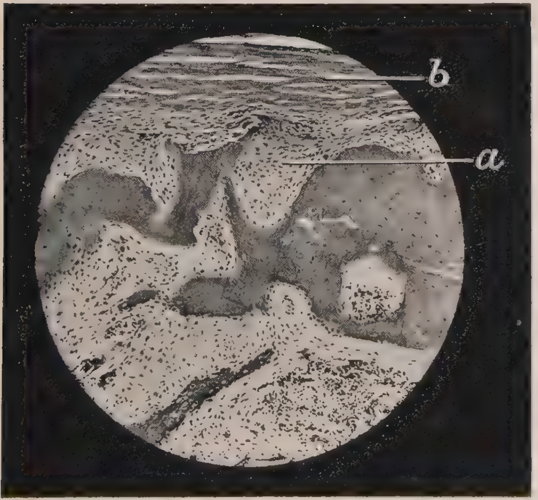

FIG. 521.—Margin of Rib in Rickets, showing irregular masses of Cellular Tissue (*a*), extending into Bone from Periosteum (*b*). × 40.

the period of active rickets almost immediately raises the retention values of the two bone-forming elements.

Pathology. It will appear from the above that the essential feature of rickets seem to be a failure to fix calcium by the osteoblasts, whilst at the same time there is no diminution in the proliferative activity of these cells; the defect is essentially in calcium metabolism. There is evidence also that when there is a condition of marked malnutrition, the proliferative activity is affected in addition; there is little formation of osteoid tissue, and the anatomical changes are rather those of osteoporosis than of rickets. This is seen, for example, in the so-called latent rickets met with in poorly nourished children.

While various factors such as amount of mineral constituents and their proportion in the diet, general hygienic conditions, confinement, etc., have been shown to play a part in the production of rickets, it has now been proved in animal experiments that a deficiency of vitamin D is the essential factor.[1] The addition of this component to a diet which has produced rickets will lead to the cure of the condition provided that the minimum amount of minerals necessary for ossification has been supplied. Mellanby was the first to show the essential part played by fat-soluble vitamin, and he also demonstrated the abundance of the vitamin concerned in cod-liver oil. For a time it was believed that vitamin A was the active substance but afterwards vitamin D was distinguished and shown to be the anti-rachitic factor. If, however, the amount of this vitamin is partially deficient in the diet, other conditions may determine the incidence of the disease. Vitamin D is specially abundant in fish oils, e.g. in cod-liver oil. It also occurs in other animal fats, milk, etc., and is fairly abundant in egg-yolk. Deficiency of the vitamin is the important factor also in osteomalacia (p. 830); further, it leads to deficiency in the growth of the teeth and predisposes to caries.

The next step in the enquiry was the demonstration that deficiency in vitamin D could be made up for to a large extent, by exposure to ultra-violet rays, whether these were derived from sunlight or from a mercury vapour lamp. This was shown both by observations on the human subject and also experimentally. It was then found that irradiation of various diets conferred on them the anti-rachitic property, that this depended on a change in the sterols associated with the fats, and that ergosterol was the substance concerned. Irradiated ergosterol is now regarded to be the pro-vitamin or mother substance of vitamin D. Ultra-violet rays produce the anti-rachitic effect by transforming the ergosterol in the skin and thus leading to the formation of vitamin D. The effects of the rays have been found to vary according to the colour of animals, pigment in the skin interfering with their action. This probably explains the fact that negro children are specially liable to rickets when placed in the surroundings of temperate climates. The time of maximum incidence of rickets, namely the late winter months, apparently depends upon the lack of sunlight during the winter. The last step in this remarkable series of researches was the separation from irradiated ergosterol of a crystalline substance now known as *calciferol.* This substance, which was obtained by English and German workers independently and about the same time, probably represents the vitamin in pure form. It possesses anti-rachitic properties far in excess of any other known body.

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[1] For details see *Vitamins: A Survey of Present Knowledge*, Medical Research Council, London, 1932, and *Recent Advances in Pathology*, 3rd edit., by G. Hadfield and L. P. Garrod, London, 1938.

Vitamin D acts mainly by leading to an increased absorption of calcium from the bowel. Whether it also influences the fixation of calcium in osteoid tissue is not certain, but the fact that in large amounts the bone formed at the epiphyseal line is of increased density suggests that it does so. In very large doses pathological effects are produced by vitamin D ; in fact in some animals death occurs after various symptoms. In this condition of *hypervitaminosis* there occurs an increase in the blood calcium along with increased excretion of calcium and phosphorus in the urine ; sometimes phosphatic calculi form in the bladder. In addition, provided that there is a sufficiency of calcium in the diet, there is often a widespread metastatic calcification, this occurring in the arteries, heart wall, kidney, stomach, etc. (Figs. 104, 105). If, along with excess of vitamin D, there is insufficient calcium in the food, the hypercalcæmia is obtained by a withdrawal of calcium from the bones, the spongy tissue of which undergoes rarefaction. The results of hypervitaminosis resemble those due to parathyroid hyperfunction (p. 955), but in the latter case the calcium is simply withdrawn from the bones. It must be understood, however, that these results have been obtained by relatively enormous amounts of vitamin D, sometimes several thousand times the therapeutic dose. And there is no evidence that the administration of vitamin D in the amounts employed in treatment has any harmful result.

Some facts may be added with regard to vitamin A, referred to above. Deficiency in vitamin A leads to a condition of xerophthalmia, and a corresponding condition is met with in children whose diet has been mainly artificial foods. In this condition, as the term implies, there is a dryness of the conjunctiva associated with a spreading opacity of the cornea. Inflammatory changes supervene and these may be followed by necrotic softening of the cornea or *keratomalacia.* There is a general effect on epithelium shown by a tendency for it to be keratinised, e.g. in the lining of ducts (p. 180). There are also impairment of growth and porosity of bones, and lesions have been described in some of the internal organs. As has been said, deficiency in vitamin A has an important effect in lowering the resistance of the tissues to various bacterial infections. It may be noted that, whilst ultra-violet radiation has a curative effect on rickets, it has no influence in xerophthalmia. The two vitamins (A and D) differ also in their resistance to heat and other agencies.

Infantile Scurvy, or Barlow's Disease. This disease is characterised by defect in bone formation and by the occurrence of hæmorrhage in connection with the bones and elsewhere. It usually commences towards the end of the first year of life, though it may occur later, and is due to the want of natural milk and the substitution of artificial preparations—in short to deficiency in vitamin C. It is essentially scorbutic in nature, and in most cases yields to treatment with anti-scorbutic remedies. It is not infrequently associated with rickets, but may occur quite apart from that disease. The view once held, that it was a form of acute rickets with a tendency to hæmorrhage, has now been abandoned, though the two diseases present certain points of resemblance.

The chief features of scurvy are present, namely, sponginess of the gums and hæmorrhage from them, hæmorrhages into the skin, muscles, and occasionally into the joints, anæmia, etc. In the bones there is defective ossification, which precedes the occurrence of hæmorrhages. The cellular red marrow is largely replaced by a somewhat œdematous fibro-cellular tissue, little bone formation occurs, and, as the normal absorption comes to be in excess, the trabeculæ already formed become thinned; hence fragility of the bone results. At the epiphyseal line the ossifying zone is deficient, and the lines of cartilage cells are invaded by blood vessels to a slight extent and irregularly. Separation of the epiphysis through the calcified trabeculæ of cartilage sometimes follows. Hæmorrhages, occasionally of large size, occur under the periosteum, which is raised from the bone. They are most frequent at the ends of long bones but may also be found in the ribs, scapula, upper wall of orbit, etc. In extreme cases the bones become very fragile and hæmorrhage may be present in their medulla. Anæmia of a hypochromic type is usually present. This is not due to the hæmorrhages but to the lack of vitamin C, the administration of which causes a reticulocytosis. Some facts as to vitamin C are given above.

Osteomalacia. This is a general disease of the osseous system in adult life, characterised by softening of the bones and resulting deformity. In the great majority of cases it occurs in women during pregnancy or the period of lactation, and in them the manifestation usually appears first in the bones of the pelvis, the softening being often preceded by dull pains. It is said to be commonest in those who have borne several children. The disease is, however, sometimes met with in young nulliparous women, and occasionally even in the male sex. It is relatively common in parts of India and China but rare in temperate countries, though it is met with on the Continent, notably in the Balkan States. After the war (1914–18) there was an outbreak in Vienna as the result of dietetic conditions, the affection being known as 'hunger osteomalacia'; it affected especially the middle-aged and old people of both sexes. Recent work has shown that osteomalacia in the adult is analogous to rickets in the child. The main factor is an abnormality in calcium metabolism brought about by insufficient supply of vitamin D. This appears to be chiefly the result of vitamin deficiency in the diet, which in India and China is of a very poor character, consisting almost entirely of cereals. In India the practice of purdah, by which women are confined to the house, also plays a part as exposure to sunlight is thus prevented. Deficiency of calcium is sometimes contributory; and in the case of pregnancy the necessary supply of calcium by the maternal tissues to the fœtus apparently acts as the precipitating cause. Osteomalacia in different places has been found to yield to the various forms of vitamin D therapy. The following are the chief structural changes in osteomalacia.

The bones undergo a gradual softening and yield to the forces of pressure and strain. Thus the pelvis undergoes a sort of collapse and becomes greatly narrowed, while the symphysis is pushed forward and assumes the form of a bill-like projection. Yielding to weight is exemplified also in the case of the vertebræ; curvatures, kyphosis and scoliosis, occur and the column becomes shortened. In a similar way the bones of the leg become bent and spontaneous fractures may take place. In extreme cases the bones become quite soft and pliable.

When the bones are examined microscopically, it is seen that most of the bone trabeculæ show a superficial and fairly well defined layer of osteoid tissue covering an osseous centre, though at a later stage trabeculæ may consist entirely of osteoid tissue. Further, the marrow becomes more abundant and encroaches on the trabeculæ, so that much thinning of them results. Similar change extends also to the dense bone of a shaft, and ultimately the compact bone is reduced to a thin shell, within which there is abundant porous osteoid tissue. Considerable proliferation of cells of the connective tissue occurs in the marrow, and a fibrillated tissue is formed, which at places merges into the osteoid tissue.

Where there is spontaneous fracture abundant soft callus of osteoid tissue is formed, but calcification does not follow. The deficiency is thus not in the proliferation of the osteoblasts, but in the laying down of lime salts. The disease may undergo cure, and lime salts are once more deposited in the trabeculæ; deformities which have been produced may thus become permanent. In portions of the bone where the disease has been specially severe, cyst-like spaces are sometimes left.

Osteitis Deformans (Paget) and Osteitis Fibrosa (v. Recklinghausen). These conditions have come to be of great interest in view of the important alterations in calcium metabolism and the relation of these to the parathyroids, which have been established with regard to the generalised form of the latter disease. The two affections correspond closely in their histological changes but the characteristic metabolic disturbance does not occur in the former. We shall first give an account of the main structural changes.

Osteitis Deformans was first described by Paget in 1876, who recorded five cases—hence it is often known as 'Paget's disease of bone.' It is commoner in men than in women and usually appears after the age of forty. It is characterised by enlargement of the bones with a certain degree of softening, and it is attended by dull aching pains and sometimes by tenderness along the bones. The bones most frequently affected are those of the lower limbs and the skull,

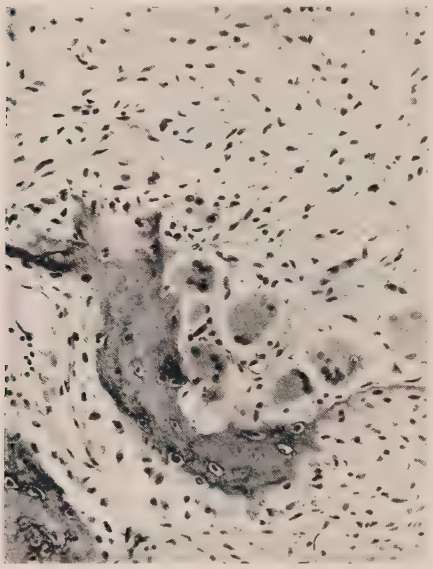

FIG. 522.—Section of Bone in Osteitis deformans, showing absorption of Bone by Osteoclasts and replacement by Fibro-cellular Tissue. × 200.

but the vertebræ and other bones such as those of the pelvis, are not seldom involved. In the case of the long bones, the shafts become thickened both outwards and inwards, so that the bone, as a whole, becomes enlarged and the medullary cavity is encroached upon. The femur and the tibia often show a forward bow-like bend owing to their yielding to the weight of the body; and the neck of the femur becomes set more nearly at a right angle to the shaft. The skull shows a progressive enlargement and the thickness of the calvarium may be three or four times the normal. The distinction between diploë and the tables becomes gradually lost, and the whole bone comes to have a fairly uniform porous appearance, while it shows a degree of softening which may be so marked that the bone can be cut. Similar changes in less degree may be present in the bones of the face. When the vertebræ are involved they yield to a certain extent, and posterior curvature occurs in the dorsal region so that the patient comes to have a sort of crouching attitude. The disease is a very chronic one and the giant-cell tumours and cysts such as frequently form in osteitis fibrosa are uncommon. Sarcoma, however, sometimes follows.

Osteitis Fibrosa. Some years after Paget published his account of osteitis deformans, a closely similar affection was described by v. Recklinghausen under the name of *osteitis fibrosa*, and he described two forms, a generalised and a localised. The generalised form is met with at an earlier period of life than Paget's disease, usually starting in adolescence. It is characterised by bone pains, softening and bending of the bones with resulting deformity; spontaneous fracture also occurs. The bones are often enlarged and, in addition, tumour-like swellings occur in them (Fig. 523). The primary and essential change is an absorption of calcium salts resulting in a rarefaction of the bones, as is shown in skiagrams. This is well

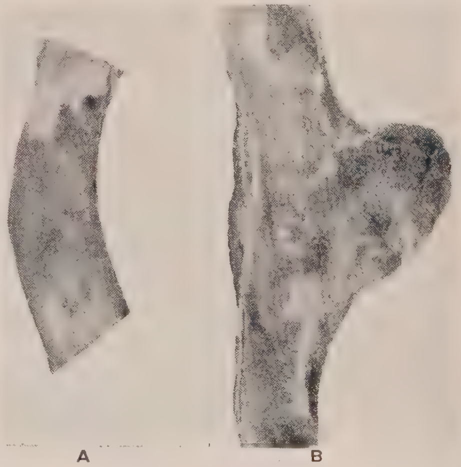

FIG. 523.—Portions of bone in Generalised Osteitis Fibrosa. × $\frac{3}{4}$.

(A) Section of calvarium, showing disappearance of diploë and uniform appearance of bone. (B) Portion of rib with osteoclastoma.

illustrated in Fig. 524. Many of the swellings come to be occupied by cyst-like spaces which may have a comparatively smooth wall; the disease accordingly is often known as *osteitis fibrosa cystica.* As compared with Paget's disease the chief differences are the earlier age of incidence in osteitis fibrosa, a greater degree of softening of the bones, resorption being in excess of formation, and also a greater tendency to the formation of cystic spaces. These facts alone would suggest that osteitis deformans is merely a more chronic form of osteitis fibrosa, but, as will be described, there is an important difference in metabolic changes and their relation to the parathyroids.

The *localised form,* which also starts in earlier years, is characterised by the formation of a tumour-like mass (osteoclastoma) in a bone; occasionally more than one may be present. The growth is usually in a long bone near the extremity of the diaphysis, but occurs also in other bones. The upper end of the femur is said to be the commonest site. Softening often occurs in the tumour mass at places, and ultimately a large cyst-like space may form. Spontaneous fracture is common.

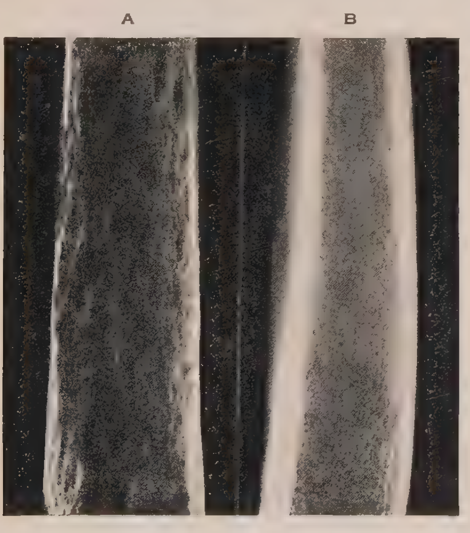

Fig. 524.—A. Skiagram of portion of femur in generalised osteitis fibrosa showing marked rarefaction of the bone. B. Skiagram of portion of normal femur for comparison. (Dr. S. V. Telfar.)

Histological Changes. As we have seen, these appear to be essentially of the same nature in these affections, and they may be said to represent a combination of absorptive and formative processes. The pre-existing bone undergoes extensive absorption; this is mainly due to the action of osteoclasts (Fig. 522), though other processes are concerned. At the same time there is an extensive growth of spindle-cell tissue which occupies the spaces between the old trabeculæ, and in this tissue there is a formation of new trabeculæ, which, however, do not undergo complete ossification but remain chiefly in an uncalcified condition. After a time the bone becomes largely replaced by this fibro-osteoid tissue, which also encroaches upon the medullary cavity and causes thickening under the periosteum. In this way, the bone as a whole becomes enlarged and the characteristic appearances as described above are brought about. Later, notably in Paget's disease, lime salts may be deposited in the new tissue, which thus becomes hardened. At certain places the fibro-cellular tissue may become specially abundant and undergo a myxomatous change with subsequent softening; hæmorrhages also may occur and be followed by a similar change. In these ways cyst-like spaces may be formed and may become confluent. Localised tumour masses, usually containing many giant-cells, may form osteoclastomata; and occasionally true sarcomatous growth has ultimately developed. Although the term 'osteitis' has been applied, it does not appear justifiable to regard the condition as of inflammatory nature, and it seems to be rather of the nature of a dystrophy. v. Recklinghausen in a second paper spoke of it as a 'metaplastic malacia,' and this designation appears suitable in our present knowledge.

It has now been established that in generalised osteitis fibrosa there is a great disturbance of the calcium metabolism in which the parathyroids are concerned, and which leads to removal of calcium from the bones (p. 953). Hypercalcæmia is present, the blood often containing 15 mg. of calcium per 100 c.c., or even more; and the phosphorus is usually low. There is a marked excess in the excretion of calcium and phosphorus in the urine. Occasionally metastatic calcification has been observed. In a large number of cases a parathyroid tumour has been found to be present; in fact, recent observations would point to this being the rule. Excision of the tumour has, in many instances, led to a disappearance of the hypercalcæmia and also to a marked change in the bones, these gradually becoming the seat of calcification in the ordinary way. In some instances tetany has actually followed immediately after removal of the affected parathyroid. This apparently means that the function of the other parathyroids was partly in abeyance, as removal of one in the normal state does not result in tetany. It may thus be regarded as established that the softening of the bones and other changes in osteitis fibrosa are the result of parathyroid hyperfunction which leads to excessive absorption of lime salts from the bones. In Paget's disease no corresponding changes in calcium metabolism have been found nor has the association of a parathyroid tumour with the disease been noted. It is suggestive, however, that in the blood a distinct increase of the enzyme phosphatase has been found, just as occurs in osteitis fibrosa. So far, no distinct disturbance of metabolism has been observed in the localised form of osteitis fibrosa.

Leontiasis Ossium. In this condition, known also as 'cranio-sclerosis' there occurs a marked enlargement of the bones of the skull and face, while the density of the bone becomes greatly increased. Swellings occur both outwards and inwards, the cavities become encroached on and the foramina are narrowed, with resulting pressure on the nerves. As in Paget's disease, the cranium becomes greatly increased in thickness, but the bone is of hard, almost ivory-like consistence. It has been suggested that this condition represents a localised form of Paget's disease which has passed into a sclerotic stage, and this appears not unlikely, although the affection develops at a comparatively early period of life. The causation of the condition is quite unknown.

Acromegaly. The changes in the bones in this disease are described below (p. 921).

Hypertrophic Pulmonary Osteo-Arthropathy. As the name implies, this condition, which was first described by Marie, is specially related to pulmonary diseases, and these are of chronic nature such as bronchiectasis, fibroid phthisis, emphysema, tumours of the lungs, etc. It is met with, however, in some other conditions, such as chronic cardiac disease, chronic jaundice, etc. It is characterised by thickening of bones due to the formation of a thin subperiosteal layer of bone, which is usually comparatively smooth, though sometimes rather irregular. There is also thickening of the connective tissue around. The bones chiefly involved are those of the forearm and leg, especially towards their lower extremities; the femur and humerus are sometimes similarly affected. The feet and hands become thickened and lengthened owing to corresponding changes in the bones. The joints in relation to the osseous changes become implicated in a certain proportion of cases, the synovial membrane being swollen and thickened, and the movement being impaired; the wrists and ankles are most frequently involved. The causation of this form of osteo-arthropathy is obscure. Toxins absorbed from the lungs or other tissues are believed by some to be chiefly concerned, whilst chronic congestion also is considered to play a part. At present, however, it is not possible to say how the changes are brought about. *Clubbing* of the distal phalanges is met with in osteo-arthropathy, but occurs apart from this affection, in conditions such as those mentioned above. The phalanges are widened and thickened, whilst the nails are raised, curved, and often fibrous in texture. The clubbing is the result of thickening of the soft tissues, which has been ascribed to various changes. Campbell describes the change as a chronic œdema of the soft tissues with overgrowth, very noteworthy under the nail-bed. We have seen his sections and agree with the description. He considers that the chief cause is deficient oxidation of the tissues with resulting œdema, and there appears to be much in support of this view.

Osteogenesis Imperfecta or Fragilitas Ossium. The former term is preferable as fragility may be due to various causes. The condition is one which usually develops during intra-uterine life, so that marked changes in the bones are present at birth; occasionally it is of post-natal origin. The most noteworthy feature is fragility, and spontaneous fractures may occur in large numbers; the bones may become irregularly broken, altered in outline, and shortened accordingly. Fractures and consequent reparative changes with cartilaginous callus may occur even before birth. Ossification is deficient also in the cranial bones, which become softer and less resistant, the transverse diameter of the skull in the temporal region becomes increased, and the ears are turned somewhat outwards and downwards. Unlike what occurs in achondroplasia, the proliferation of cartilage cells at the epiphyseal line goes on as usual, and ossification occurs in a regular manner, but there is marked deficiency in the amount of bone formed. The compact bone on the surface forms a thin layer, while the trabeculæ are narrow and widely separated, the whole appearance being as if the osteoblasts had defective powers of bone formation (Fig. 525); this applies both to intramembranous and to endochondral ossification.

In many cases the child affected with the disease in its extreme form dies shortly after birth; in less severe cases a tendency to spontaneous fracture may persist for some years and then gradually pass off Here also some endocrine deficiency has been suspected, but no definite facts have been established and the true etiology is unknown.

In some instances the disease is of hereditary and familial type, and the term *familial fragility* has been applied. An account of two families in which there were several cases of osteogenesis imperfecta has been given by Bronson. In this type fractures are not so numerous and do not occur so early as in the non-familial type. The tendency to fracture is often attended by 'blue sclerotics,' a condition due to an abnormal translucency of the sclerotics. Deafness due to otosclerosis often develops towards adult life and there may be also an undue looseness of ligaments of joints. Apart from the hereditary element nothing is known with regard to the causation of the affection.

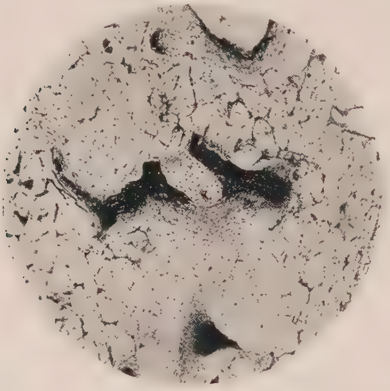

FIG. 525.—Section of Bone in Osteogenesis Imperfecta, showing isolated and imperfectly formed Trabeculæ. × 30.

Achondroplasia. This remarkable condition, which is known also as *chondrodystrophia fœtalis*, is characterised by failure of endochondral ossification. It is present at birth and the child presents certain characteristic features. The head appears large and the root of the nose is indrawn or sunken; the limbs are short and stumpy, sometimes curved, and as there is more growth of the soft tissues than of the bones, the skin of the limbs is in folds. There is usually a considerable amount of fat, and sometimes there is some œdema. The characteristic changes depend on one essential lesion, namely, failure of the process of bone formation in cartilage. At the position of the epiphyseal line, the cartilage cells form only short rows, or may be irregularly arranged and there is little or no ossification, hence the diminution in the length of the bones. The cartilaginous epiphysis is sometimes considerably enlarged, and with the small shaft presents a mushroom-like appearance; there may be also areas of softening in the cartilage. The indrawing of the nose results from a shortening of the base of the skull, and this also is due to imperfect ossification, which is sometimes accompanied by premature union of the basi-sphenoidal and sphenoidal sutures. In fact, all the bones ossified from cartilage are deficient, whilst the intramembranous ossification proceeds quite normally (Fig. 526). There are varying degrees of the condition, and whilst the child often dies within some weeks after

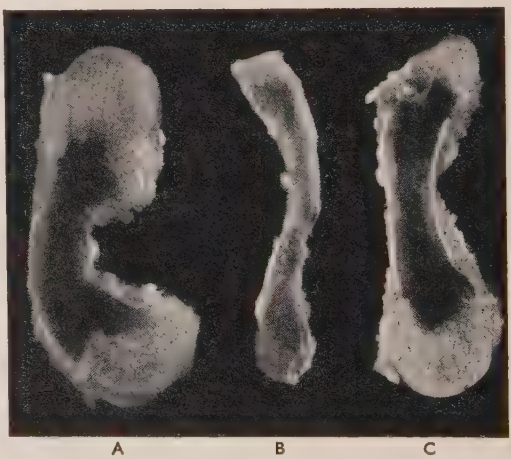

FIG. 526.—Bones from a case of Achondroplasia (natural size).

(A) Femur. (B) Clavicle (for comparison). (C) Humerus.
(J. W. S. B.)

birth, in less severe cases it may survive to adult life as a form of dwarf with short thick limbs, but with no other important change. Nothing definite is known of the etiology of this condition. One naturally suspects deficiency in the endocrine glands, but no definite lesion has been found in any of them. The condition has sometimes been called 'fœtal rickets,' but the lesions are of quite a different nature from those in rickets. It is also clearly distinct from cretinism, as regards both the condition of the thyroid and the lesions in the bones.

Cretinism. The osseous changes in this condition are described below (p. 933).

Diaphyseal Aclasis. This term is applied to a condition where there is a disturbance of ossification at the epiphyseal ends of long bones, both enchondral and periosteal processes being involved. The normal growth in length is impaired and when there is multiple affection of bones a certain amount of dwarfism may result. The metaphysis is also broadened owing to failure in the normal moulding, and from its surface outgrowth of cartilage occurs, forming chondromata. These undergo ossification and become rounded or pointed osteomata; they are covered with a layer of cartilage till the period of complete ossification. The disease is hereditary in most cases and the condition is also known as *hereditary multiple osteomata.* A closely allied condition is *dyschondroplasia* or *Ollier's disease*; the relation of the two affections is still in dispute. Nothing is known as to etiology.

Lipoid Granulomatosis or Xanthomatosis of Bones. This is an example of disturbance of lipoid metabolism similar to that described above in other affections (p. 499). It is characterised by the formation of multiple nodules especially in bones ossified in membrane, notably in those of the skull. The condition, which thus simulates multiple tumours, is due to localised accumulation of lipoid within reticulo-endothelial cells; it has been met with chiefly in infants and young children. The lipoid involved in cases reported has been cholesterol esters and the affection may be regarded as an example of the Hand-Schüller-Christian disease.

TUMOURS

Simple Tumours. The *osteoma* and *chondroma* are the characteristic simple growths of bone, and these have already been described (pp. 211, 212). *Fibroma* occasionally occurs in connection with the bones of the jaws; the alveolar margin of the lower jaw is a not uncommon site, the tumour being then known as *fibrous epulis.* It usually grows from the periosteum and often contains spicules of bone. Transitional forms to sarcoma also are met with. *Myxoma* is a rare tumour in bone, but is seen sometimes, especially in the medullary cavity, where it may reach a large size. The so-called *cysts of bone* may result from softening of a tumour, for example, a myxoma or chondroma. Cystic

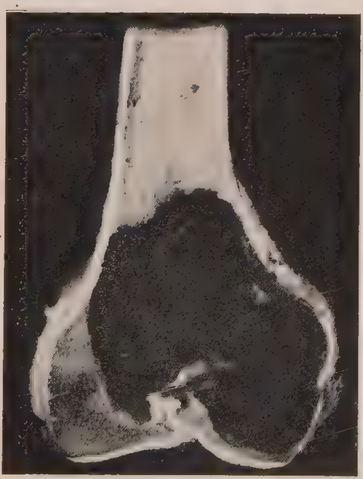
FIG. 527.—Cyst-like space in lower end of Femur, resulting from softening of Myeloid Sarcoma.

spaces sometimes occur in bone in connection with Paget's disease and osteitis fibrosa (p. 833), and also apart from these affections. Such cysts are often elongated in form, contain brownish fluid and are lined by a fibro-cellular tissue in which giant-cells are present. As already stated, it is not possible to draw a line between such cystic growths and what may be called a localised form of osteitis fibrosa. A space containing altered blood not infrequently arises from the softening of the interior of a myeloid sarcoma (Fig. 527).

Malignant Tumours. The primary growths may be briefly summarised as follows: (*a*) By far the commonest is the *true bone sarcoma* often known as '*osteogenic sarcoma*,' a growth originating from osteoblasts. (*b*) Another well recognised though much less common variety is *Ewing's sarcoma*; its origin is doubtful. (*c*) *Giant-cell sarcoma*, *myeloid sarcoma* or *osteoclastoma*; it is rarely malignant and is sometimes placed by writers amongst the simple growths. It may best be regarded as being a type by itself.

Multiple myeloma is often placed amongst the bone tumours, but its origin is from the cells of the marrow. Its characters have already been described (p. 519).

[1] **Bone Sarcoma or Osteogenic Sarcoma.** This, which is by far the commonest tumour of bone, is met with especially during the period of growth and early adult life. In fact after the age of thirty it is comparatively rare. It arises most frequently in the metaphysis of a long bone, being specially related to endochondral ossification. Sarcoma in bones ossified in membrane is comparatively rare. It occurs much more frequently in the lower limb than in the upper, the lower end of the femur and upper end of the tibia being specially common sites. In the upper limb the upper end of the humerus is the commonest site. Sarcomata vary much in character, sometimes being soft and cellular and reaching a great size, sometimes being firm, or even hard owing to bone formation, as occurs in the osteosarcomata. They usually start near the surface of the bone—the so-called *periosteal sarcomata*—and in most cases are highly malignant, bursting through the periosteum, invading the muscles, and giving rise to metastases. Periosteal sarcoma may be mainly limited to the surface and grow around the bone, but usually it extends to the medullary cavity and may spread widely within it. Much variation is met with, as regards both the size of the tumour and the rate of growth. The formation in such sarcomata of bony spicules which are radially arranged, is a common feature and this gives rise to characteristic appearances on X-ray examination. Bone sarcoma often causes much resorption of bone and spontaneous fracture may occur (Fig. 528). Sometimes the tumour forms a hard bony mass, ensheathing the bone—the so-called sclerosing type. Much less frequently a sarcoma starts deeply and leads to expansion of the bone—central

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[1] For details see *Bone Sarcoma*, by A. Kolodny, Chicago, 1927.

sarcoma. It may be noted that whilst sarcomata, as a rule, produce marked swelling of the bone, this is not always the case. We have seen a chondrosarcoma invading and replacing the bone with scarcely any swelling as the result, and there are cases where the growth extends for some distance in the medullary cavity before producing enlargement; these, however, are rare. Occasionally there is abundant formation of blood vessels in a bone sarcoma; 'teleangiectatic type,' and even pulsation may be present.

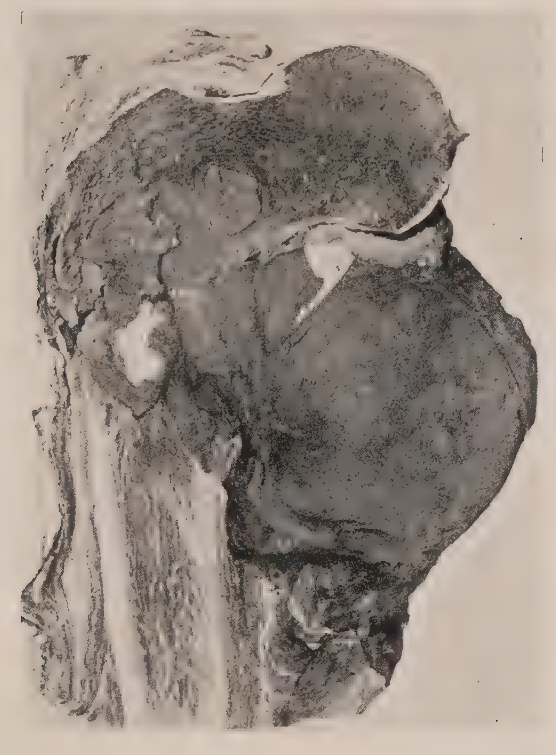

Fig. 528.—Large Sarcoma of upper end of Femur.

Note the absorption of bone which has led to spontaneous fracture, the neck being almost at right angles to the shaft. × $\frac{2}{3}$.

The *histological characters* also vary greatly. The commonest type of periosteal sarcoma is the small spindle-cell sarcoma, but mixed-cell and round-cell sarcoma, chondrosarcoma, osteoid sarcoma and osteosarcoma also are met with (pp. 230, 231). Matrix may be delicate and scanty or it may be abundant—fibrous, mucinous, osteoid, etc. All these tumours arising from bone cells are highly malignant; they form metastases at an early date, usually first in the lungs, and the prognosis is very bad. Endothelioma and perithelioma occur also, and some of the examples of the former correspond with what used to be described as alveolar sarcoma.

Extra-Periosteal Fibrosarcoma. This is a somewhat rare tumour which grows from the outer layers of the periosteum and may stimulate an osteogenic sarcoma. It is composed of spindle cells with a varying amount of fibrous matrix and remains localised for a considerable time; it causes little or no resorption of bone. The prognosis is relatively favourable, though ultimately infiltration of surrounding parts and metastases may occur.

Ewing's Sarcoma. This is now a well recognised growth and is not uncommon, constituting, according to American statistics, about ten per cent. of all primary malignant tumours of bone. It usually arises in the interior of the diaphysis of a lone bone, the tibia being the commonest site; occasionally it occurs in a short bone, especially the calcaneum. The period of incidence is the same as that of osteogenic sarcoma. The tumour is composed of soft cellular tissue, often of necrotic appearance. It leads to resorption of the surrounding bone and extends outwards along the Haversian canals; there then occurs reactive formation of bone by the periosteum, the new bone being laid down in layers and leading to thickening of the shaft. A characteristic appearance is thus produced. The starting of the growth is often attended by deep-seated pain and a certain amount of pyrexia and leucocytosis.

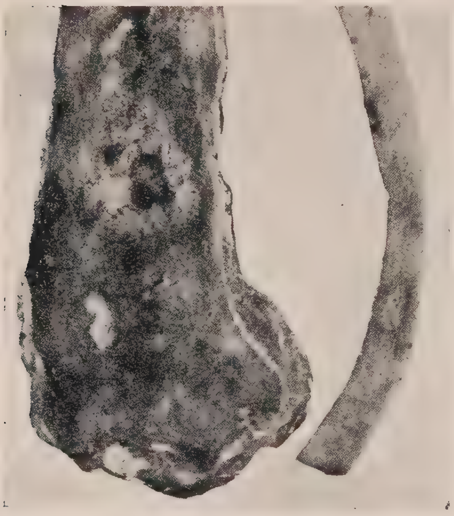

Fig. 529.—Carcinomatous Invasion of lower end of Femur and of a Rib, secondary to Carcinoma of Prostate.

The rib is shown on section, and it is seen that the medulla has been replaced by dense sclerotic bone; the femur shows irregular early areas of similar nature.

Microscopic examination shows that the growth is composed of rounded or polyhedral cells with rather ill-defined protoplasm; stroma is very scanty and of fine character. The cells are arranged in irregular masses or sometimes in a perithelial manner round blood vessels. Considerable variations in the histological features are met with. The site of origin of the growth and the fact that the cells do not form bone indicate strongly that it arises from the marrow, probably from reticulo-endothelial cells, and is thus not a true tumour of bone.

Metastases form in the lungs and other organs though often somewhat late. An important fact is that they occur also in other bones, a rare site for secondary growths in the case of osteogenic sarcoma. Some of the growths may be of independent origin. A feature of the tumour is its susceptibility to radiation (Ewing) but recurrence usually follows and a fatal result is the rule.

Myeloid sarcoma, the features of which have already been given (p. 231), usually produces merely local destruction of bone and metastases are quite exceptional. It is to be noted that the *myeloma* proper, a multiple round-cell growth which leads to destructive softening of bones, really springs from the cells of the blood-forming marrow. It is described on p. 520.

Secondary growths of carcinoma are not infrequently met with in bones, occasionally also secondary sarcoma. Melanomata are specially prone to give rise to metastases, which are sometimes very numerous. In the case of cancer, secondary growths occur especially in cancer of the breast, prostate, and thyroid; they are also met with in kidney tumours, both hypernephroma and papillary adenocarcinoma. The reason for this incidence is not known. They may be in large numbers and practically any bone may be affected, although the bones containing red marrow, notably the vertebræ and ribs, are specially liable to be involved. Secondary growths vary in their effects and are sometimes described as *osteoclastic* and *osteoplastic*. In the former, great resorption of bone is the chief feature, and spontaneous fracture may occur; whilst in the latter the effect is mainly a thickening and sclerosis of the surrounding bone which encroaches on the marrow (Fig. 529) and leads to anæmia—*osteosclerotic anœmia*.

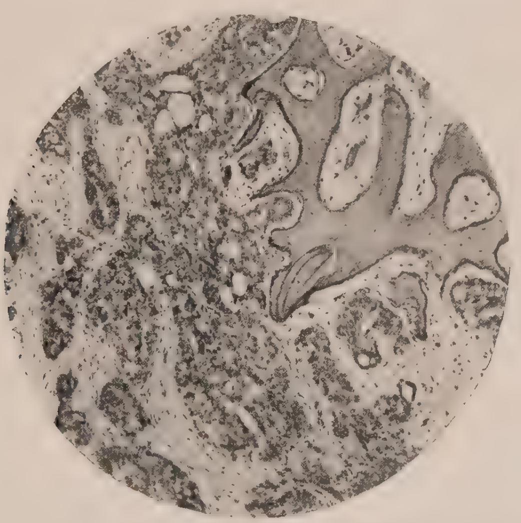

Fig. 530.—Section of Bone in a case of Prostate Carcinoma, showing the diffuse infiltration by Cancer Cells. (A. A. C.) × 60.

Tumours of Joints. Primary tumours of joints are of great rarity. Primary sarcoma has been described, but sarcoma in a joint is usually secondary to the growth in bone. The fatty, cartilaginous, and osseous growths met with in certain chronic diseases are, of course, not to be regarded as true tumours.

Myeloma of Tendon Sheaths. Small tumour-like masses of tissue are sometimes found in connection with sheaths of tendons, in which giant-cells are present along with a fibro-cellular tissue ; foamy cells containing fatty material, the so-called 'xanthoma cells,' are sometimes a prominent feature, and there may be also a considerable accumulation of hæmosiderin. Such growths, which are usually known as 'myelomata of tendon sheaths,' are, as a rule, of quite simple character, in fact some of them correspond in structure with a reactive rather than a neoplastic process ; but in some instances they have displayed malignant properties and given rise to metastases. This has occurred especially in those connected with larger tendons, and sometimes the malignant growth has been composed of the xanthoma cells ; the term *xanthosarcoma* has then been applied.

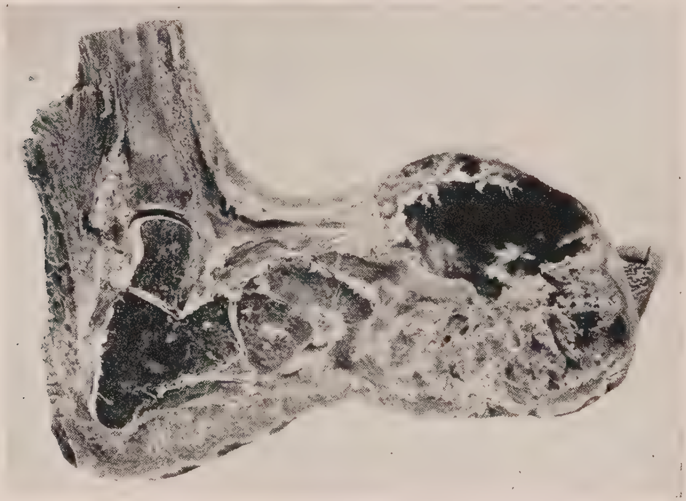

FIG. 531.—Large Myxosarcoma of anterior portion of Foot, showing central softening and cavity formation.

B. JOINTS

Acute Arthritis. Apart from the acute inflammatory swelling of the soft tissues of a joint produced traumatically by contusion or strain, acute arthritis is, in the vast majority of cases, the result of an infection by way of the blood stream. Two types of acute arthritis are usually distinguished—the *non-suppurative* and the *suppurative* ;

and the distinction is of importance in view of the difference in results. Of non-suppurative acute arthritis, the rheumatic and the gonorrhœal are the outstanding examples, but the latter may also be of the suppurative type.

Rheumatic Arthritis. In *acute rheumatism* several joints are usually affected, and as the condition resolves in some, others often become affected. There is general acute inflammation of the synovial membrane, with effusion into the joint cavity, and the fluid in excess has a more or less turbid appearance owing to the presence of leucocytes and sometimes shreds of fibrin are present. The *Micrococcus rheumaticus* has often been cultivated from the joints, but as a rule no organisms can be found on microscopic examination of the fluid ; and this is usually explained as being due to the fact that they flourish especially in the substance of the synovial membrane. The most important inflammatory changes are in the latter and occur partly in the form of focal inflammations as elsewhere, and partly as a general affection of the soft tissues. It may be stated that, although the disease is by many believed to be due to the organism mentioned, this view is not universally accepted. In the majority of cases the inflammation subsides completely, and there is a return to normal, but sometimes, especially when the substance of the capsule is involved, it passes into a sub-acute and chronic condition, and there may be permanent thickening of the capsule and the tissues around. Along with the affection of the joints, inflammatory foci, known as 'subcutaneous nodules,' may occur under the skin, and also in the inter-muscular connective tissue, periosteum, etc. They are met with especially in children and are usually of evanescent character, though some may remain as fibrous nodules (*vide* p. 849). Inflammatory changes may take place in other parts of the body. Endocarditis is a common complication (p. 344), and there are inflammations of serous membranes, especially of the pericardium, also of the pleura. In all these positions inflammatory foci and formation of Aschoff bodies as described in connection with the myocardium (p. 332) may be present. Acute rheumatism may be attended by symptoms of cerebral irritation, known as 'cerebral rheumatism,' and this may be followed by hyperpyrexia. It is occasionally followed by chorea, especially in children, though this disease may occur independently. Chorea results from an infection of the brain and there are found infiltrations of round cells around the minute vessels along with a certain amount of endothelial proliferation. Such small lesions are present chiefly in the cortex and in the corpus striatum. It may be added that the onset of acute rheumatism is often preceded by tonsillitis or sore throat, and it is probable that the infective agent gains entrance by the fauces.

Gonorrhœal Arthritis. Sometimes, especially in the later subacute stage of gonorrhœa, gonococci are carried from the urethra by the blood stream to other parts, and they show a special tendency to infect joints, tendons, and other fibrous tissues. One or several of the joints may be affected, and the changes present are of a similar nature to those described above, but there is greater tendency for the surrounding tissues to be involved. Not infrequently tendon sheaths are affected—gonorrhœal tenosynovitis. The affection occurs in two main types, an acute and a less acute or chronic. In acute cases the joint shows the ordinary signs of inflammation, and gonococci may occasionally be found within the polymorpho-nuclear leucocytes which abound in the synovial fluid, though more frequently they are obtainable only in culture. Sometimes, however, the presence of the organisms cannot be demonstrated, owing to the fact that they flourish especially in the synovial membrane and soon undergo dissolution in the joint fluid. Complete return to normal may occur, but the condition tends to be of an obstinate character, and fibrous thickening of the capsule of the joint with adhesions may follow ; even fibrous ankylosis may result. Occasionally there may be overgrowth of bone in connection with the joint. In the less acute or chronic cases several joints are often affected and great disability may result.

Infection of a heart valve may occur in cases of blood infection, but this is of great rarity—unlike what obtains in the case of acute rheumatism. Gonorrhœal endocarditis is usually characterised by large crumbling vegetations.

Suppurative arthritis may occur in systemic infection with a variety of organisms, but streptococci and staphylococci are chiefly concerned. Pneumococcal arthritis is met with in children ; it is usually not severe and suppuration may not follow. There may be some suppuration or inflammatory infection elsewhere, such as erysipelas, puerperal sepsis, bacterial endocarditis, etc., but in some cases the path of infection is quite obscure. One or several joints may be infected, and all degrees of severity are met with ; especially severe are the cases due to *Staphylococcus aureus*, which sometimes reaches the joint from osteomyelitis.

In some cases the condition is merely a purulent synovitis, and even with pus in the joint, resolution may occur ; but in the more severe types, suppurative foci or diffuse suppuration may form in the joint capsule and in the soft tissues around. Softening of the ligamentous structures, erosion or necrosis of the cartilage, and ultimately complete disorganisation of the joint may then follow.

Arthritis, either suppurative or non-suppurative, occurs as a complication in various specific fevers ; for example, in scarlet fever, where the affection may resemble that in acute rheumatism. In pneumonia and other pneumococcus infections, and in cerebro-spinal fever, the joints occasionally become infected with the corresponding organisms, and the arthritis may have a purulent character. Acute arthritis occurs in dysentery, less frequently in typhoid, and occasionally also in other infections caused by the organisms of the coli-typhoid group.

Chronic Arthritis. This may be the sequel to one of the forms of acute arthritis already described, especially to the rheumatic and the gonorrhœal; and chronic disease of joints is frequently due to tuberculosis, and occasionally to syphilis, as has been described in connection with diseases of bones (pp. 817, 823). In a considerable proportion of cases, however, the affection is of a chronic progressive nature throughout, and is not due to any of these causes. In the absence of knowledge as to the etiology of such conditions, classification has to be based on the structural changes and general clinical features, and there is considerable variation in the accounts given by different authorities. Two main types are, however, generally recognised:

(*a*) In one—*rheumatoid arthritis*—several joints are affected; the disease starts in the capsule of the joint and leads to interference with movement and often to ankylosis.

(*b*) In the second—*osteo-arthritis*—the primary lesion is in the cartilage or bone, and there is a combination of atrophic change with the formation of considerable outgrowths of bone and cartilage; not infrequently only one joint is affected.

But in addition to these two main types, it must be recognised that there are other conditions which vary somewhat in character and which often appear to be related to chronic septic conditions in other parts of the body. In some such cases organisms have been described, but bacteriological examination usually gives negative results, and no organism can be said to be established as a causal agent. Such conditions are included by Stockman under the heading of 'chronic infectious arthritis of unknown origin.'

Rheumatoid Arthritis or Arthritis Chronica Adhesiva. The disease may be said to be a chronic polyarthritis, as there is sometimes almost a general affection of the joints; and it starts in the soft tissues of the joints, the cartilage and bone being secondarily affected. It occurs much more frequently in women than in men, and usually begins in the years 25–40, though also at both an earlier and later period. It is, as a rule, of insidious origin and chronic throughout, though sometimes it is ushered in with more acute symptoms and some pyrexia. It has the features of a specific infection, but the exact causal agent is unknown. As antecedent conditions, physical and mental strain, abnormal gastro-intestinal fermentations, uterine disorders, dental caries, etc., have been described in various cases, but nothing definite has been established as regards etiology. The small joints of the fingers, especially some of the interphalangeal joints, are usually affected first, the disease then extending to other bones of the hands and implicating a varying number of the large joints also. There is little effusion, but the synovial membrane and the tissues around become swollen, owing to chronic inflammatory change with proliferation of connective tissue cells and formation of new blood vessels; and the joint thus comes to assume a spindle-like form. The swollen tissues then become more fibrous and indurated, and the parts around, including the tendons, are similarly involved; movement, of course, becomes markedly interfered with, and secondary changes take place in the articular cartilages. Degeneration and fibrillation occur in the cartilage, which becomes invaded by new connective tissue and blood vessels, and is gradually absorbed. There is ingrowth of granulation tissue both from the synovial membrane at the periphery and also from the bone beneath, and the joint cavity gradually becomes obliterated by the growing together of the layers. Ultimately fibrous ankylosis takes place and this may be followed by bony ankylosis. When these changes are going on in the joint, atrophic processes occur in the bone, with resulting rarefaction or porosity. Marked atrophy of the muscles sets in early in the disease and the extensors are specially affected, so that there may be partial flexion at the joints. The hand, with its atrophied muscles, contractures, and swollen joints, thus assumes a characteristic appearance. In the neighbourhood of a joint there may be marked induration of the connective tissue, and the disease is often associated with fibrositis and panniculitis (p. 849).

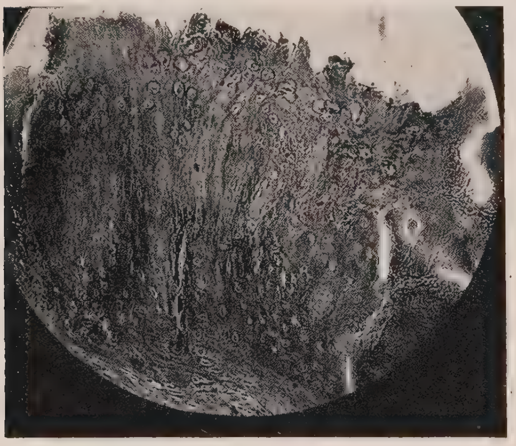

FIG. 532.[1]—Section of Cartilage in Osteo-arthritis, showing marked Fibrillation of its Matrix. (Prof. Stockman.)

Osteo-arthritis or Arthritis Deformans. This is a chronic disease of insidious origin and slow course, which affects primarily the cartilage and underlying bone. It starts usually in late adult life, though sometimes at an earlier period, and is commoner in men than in women. The larger joints are most frequently involved—occasionally several, sometimes only one, especially the hip in old men (the condition known as *morbus coxæ senilis*). The disease is occasionally met with also as a multiple affection of the small joints of the hands and feet.

The joint cartilage at an early period loses its smooth surface, becomes slightly irregular or velvety owing to perpendicular fibrillation of the matrix, and is gradually worn away (Fig. 532). The underlying bone becomes gradually exposed, and not infrequently there is parallel scoring or grooving owing to the movements (Fig. 533). The surface of the bone becomes smooth and hard or eburnated, and there are important changes in its substance. There is at places atrophy of the bone trabeculæ, whilst between them there is an excess of mucoid or fibrous marrow; the supporting power is weakened and the bone falls in at places. For example, in the hip-joint the head tends to become flattened and the neck shortened. At the same time there is new formation of bone which results in excrescences covered with cartilage (Fig. 534); these form irregular nodular projections especially at the margin of the articular surfaces, though they occur also as irregular, flattened elevations on the joint surface. In these ways great deformity and interference with movement result. The ligaments become softened and weakened, and luxation of the joint may follow. Neither fibrous nor bony ankylosis, however, occurs. Numerous vascular villous projections may form from the synovial membrane and become infiltrated by adipose tissue, and the inner surface may be beset with them—the term *lipoma arborescens* has been applied to the condition. This is especially the case when the knee-joint is affected, and the articular surfaces may be encroached on by the villous synovial membrane (Fig. 535). Cartilaginous nodules also

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[1] I am indebted to Professor Stockman for Figs. 532–534.

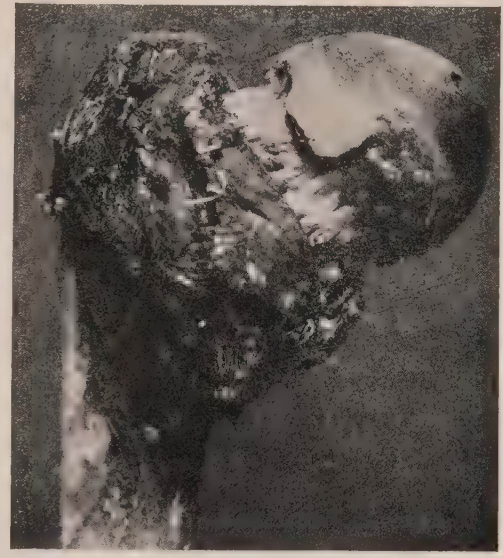

FIG. 533.—Upper end of Femur in Osteo-arthritis, showing the eburnation and grooving of the Head and irregular growth of Bone and Cartilage at the margins.

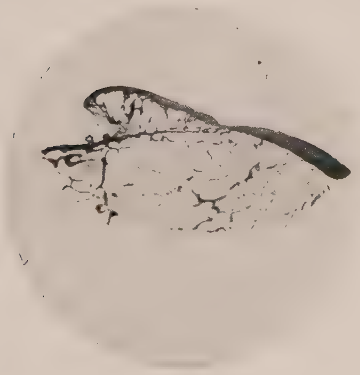

FIG. 534.—Section through Bony Elevation in Osteo-arthritis, showing delicate spongy Bone covered with thin layer of Cartilage.

may form in the villous projections and become the seat of central ossification; some of these may become detached and set free in the joint and are known as 'joint-mice.'

Considerable dispute has taken place as to whether cartilage or bone is the seat of the first lesion in osteo-arthritis, most writers speaking in favour of the cartilage. But it seems to us that the changes in the bone are too great to be merely secondary to a lesion of the cartilage, and they may be marked when the latter is little altered. It would appear from the lesions present as if the nutrition of both cartilage and bone was affected independently by the same cause. As to the true etiology nothing definite is known, although in the case of affection of a single joint traumatism seems sometimes to play a part. There is no evidence that the condition is a bacterial infection. The occurrence of somewhat similar changes in the joints in tabes and syringomyelia is suggestive of a nervous origin, but there is no definite evidence of this.

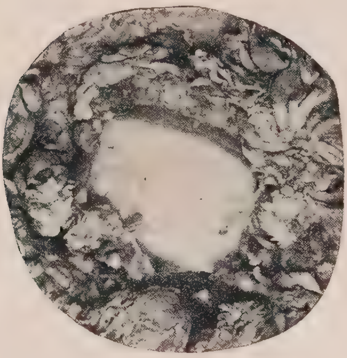

FIG. 535.—Portion of Knee-joint in Osteo-arthritis.

The patella seen from behind is surrounded by numerous villous projections from the synovial membrane.

Spondylitis Deformans or Ossifying Spondylitis. In this condition the various ligaments of the vertebræ undergo progressive ossification so that the spinal column becomes immobilised and ultimately rigid. Corresponding changes occur in the ligaments of the costo-vertebral articulations and occasionally also in the large joints of the extremities, and bony ankylosis of the affected joints may result. The affection has usually been regarded as of the same nature as osteo-arthritis but, as pointed out by Stockman, the parts affected are different in the two diseases—the fibrous tissue in spondylitis, the bone and cartilage in osteo-arthritis. Moreover, in the latter bony ankylosis does not occur. He regards the essential feature of the disease to be the formation of bone in chronically inflamed connective tissue of joints and ligaments and finds that, as regards its conditions of occurrence, it is related to fibrositis and rheumatoid arthritis. The cause of the condition is not known, as is also the reason why the ossifying process should occur specially in connection with the vertebral column.

Heberden's Nodes. These are small bony elevations or knobs which are met with on the terminal phalanges of the hands just above the joints; they may occur on one or on several fingers. Their presence interferes mechanically with movement, and the phalanx may be laterally deviated; beyond the disfigurement they are of little importance. They occur chiefly in the later years of life. Some writers regard them as a mild form of osteo-arthritis, but they are without the characteristic features of that disease.

Loose Bodies. These are of various kinds and some of them have already been described. The following may be summarised as the main types: (*a*) Multiple soft bodies—known as 'rice bodies' or 'corpora oryzoidea,' which consist either of masses of fibrin or necrotic fragments of granulation tissue; these are met with especially in tuberculous affections. (*b*) Separated hypertrophic villi of the synovial membrane, which are often of the nature of fatty lobules; they occur in chronic arthritis and osteo-arthritis. (*c*) Multiple hard bodies, which are portions of cartilage often containing bone in their interior, and which become separated from the joint margins or form in the synovial fringes—the so-called 'joint-mice'; they are met with especially in osteo-arthritis. (*d*) Portions of normal structures separated traumatically; a loose semi-lunar cartilage in the knee-joint is the commonest example.

Chronic Rheumatism. Fibrositis and Panniculitis.[1] The term chronic rheumatism is applied in a general way to conditions of chronic nature where the chief symptoms are pain and stiffness either of the joints or muscles—articular and muscular rheumatism. The latter condition has been fully described by Stockman and has been shown to be due to the occurrence of chronic inflammatory foci in the fibrous tissue, and hence the term *fibrositis* is appropriate. From an examination of sections, we can fully confirm his observations. Such inflammatory foci occur not only in the fibrous tissue of muscles but also in the subcutaneous tissue, the periosteum, ligaments, sheaths of nerves, etc. In the early stages the condition is one of an acute inflammatory œdema with swelling of the connective tissue fibres; sometimes the exudate is sero-fibrinous and there may be some central necrosis. Later, there is proliferation of the connective tissue cells and formation of collagenous fibres, so that the area affected becomes dense and sclerosed. Small arteries in the new tissue show thickening of their walls and the nerve twigs also may be involved in the newly formed tissue. There is, however, a remarkable absence of emigration of polymorpho-nuclear leucocytes, and only a few lymphocytes are usually present in the foci. No organisms have been found, and it is doubtful whether the lesions are due to the actual presence of organisms or simply to toxic action. Such lesions may occur in nodules or in strands, or be of a more diffuse character. Fibrositis, which is a common affection, is produced by a variety of conditions, and Stockman gives the following as the chief. It may occur secondarily to acute rheumatism or gonorrhœal infection, and it is not uncommon as a sequel to influenza. It is common in cases of rheumatoid arthritis and may be widely distributed; and it appears to be related to chronic bacterial infections—for example, those of the throat or bladder—and also to mucous colitis.

The term 'panniculitis' is applied to a similar condition affecting the adipose tissue, the fibrous overgrowth being in patches or more diffusely arranged in the fat. The peripheral nerves become involved and thus tenderness and pain are prominent features. It may be associated with obesity, the condition 'adiposis dolorosa' (Dercum) being an extreme example; but it occurs also apart from obesity.

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[1] See *Rheumatism and Arthritis*, by Prof. R. Stockman. Edinburgh, 1920.

C. VOLUNTARY MUSCLES

Striped muscle fibres are comparatively stable structures and are relatively seldom the seat of disease. We may say that the most important lesions include the three following conditions, namely: (*a*) The spread of inflammatory changes from the interstitial tissues, (*b*) the degenerations secondary to lesions of the nervous system, and (*c*) the primary myopathies and other congenital conditions. The changes in the muscles of neuropathic origin have been considered in connection with diseases of the nervous system and need not be described again.

Atrophic and Hypertrophic Changes. The various types of atrophy are well exemplified in the case of muscles—senile atrophy, atrophy from disuse, toxic and starvation atrophy, neuropathic atrophy, and the primary muscular atrophies which will be described below. In many of these cases there is merely a diminution in the size of the muscle fibres; but in neurotrophic atrophy and sometimes in inactivity atrophy, for example, that resulting from joint disease, there is often a longitudinal proliferation of the sarcolemma cells and a splitting of the fibres. These changes may then be followed by absorption and disappearance of the sarcous substance. The sarcolemma cells are sometimes seen to have a phagocytic action towards damaged muscle, and may occasionally form plasmodial masses with multiple and irregular nuclei. We have found a striking example of this in sprue, where the wasting of the muscles is very extreme. The phagocytic action of the sarcolemma cells towards damaged muscle corresponds with that seen in the absorption of the tadpole's tail, as described by Metchnikoff. Hypertrophy of muscle fibres is seen as the result of hard physical labour, athletic training, etc.; individual fibres become enlarged owing to increase of the sarcoplasm, but there is no formation of new fibres. In some of the myopathies abnormally large fibres are often met with; they are often spoken of as hypertrophied and may represent a compensatory process. Not infrequently they come to have a somewhat homogeneous appearance and present evidences of degeneration.

Degenerations in muscles are not common and are of relatively little importance. Zenker's degeneration (p. 559), a form of coagulative necrosis, is met with especially in the abdominal muscles in typhoid fever. The affected muscles may sometimes be recognised by the naked eye from their pale hyaline appearance. In influenza also necrosis may occur in the abdominal muscles and may be attended by a considerable amount of hæmorrhage. A somewhat similar lesion has been found in the muscle fibres in cases of tetanus. When involved in surrounding inflammatory change, the muscles may lose their striation and become somewhat granular in appearance—a change allied to cloudy swelling. A similar granularity occurs as a preliminary stage to fatty degeneration, which, however, is not often met with. The latter is seen in phosphorus poisoning, and patches of granular and fatty muscle fibres are found also in acute peripheral neuritis (p. 797).

Inflammatory Changes. Striped muscle becomes secondarily implicated by acute and chronic inflammation of the interstitial tissue, and this is often the result of extension from a lesion in the vicinity. The changes vary according to the nature of the inflammatory change. Thus in acute inflammation, œdema and necrosis of the muscle followed by absorption are prominent features, whilst in chronic inflammation there is fibrosis with atrophy and disappearance of the muscle fibres. An important acute lesion of muscles is seen in *gas gangrene*, a common occurrence during the war (1914–18). In this condition the muscles are invaded by anærobic organisms, the commonest being the *B. welchii*, the toxins of which diffuse within the sarcolemma and lead to œdema with necrosis of muscle fibres in their whole length ; thus necrosed and healthy fibres may be seen lying side by side. Later, the muscles become invaded by putrefactive organisms and gangrene follows. *Suppuration* in muscle is usually the result of extension from other suppurative lesions, especially of joints and bones. The metastatic type, due to infection by the blood stream, is met with in pyæmic conditions, especially those due to the staphylococcus aureus ; but its occurrence is relatively uncommon. The abscesses are usually of the miliary type, but occasionally suppurative lesions of considerable size may be produced. It may be mentioned also that in the rare occurrence of *acute glanders* in the human subject, multiple lesions in the muscles are sometimes a prominent feature ; they are of the nature of necrotic and partly hæmorrhagic foci, which undergo suppurative softening.

Muscular rheumatism, which is really an interstitial lesion, has been described above (p. 849).

Congenital Torticollis. This is a condition of fibrosis and contraction of the sterno-mastoid muscle which develops in the early years of life. As the muscle does not elongate in association with the general growth of the body, the head is drawn to the affected side and other results are produced. It has long been regarded either as a developmental abnormality or as the result of injury at birth ; the latter view has, however, now been established. It would appear that the essential factor is venous thrombosis or rupture of veins, which leads to intense venous engorgement and hæmorrhage into the muscle. The muscle becomes largely necrotic and replaced by young connective tissue. The result is a ‘ sterno-mastoid tumour ’ which becomes evident a few days after birth.

Shrinking of the fibrous tissue and failure in growth of the muscle then gradually bring about the deformity.

Volkmann's Contracture. This is a deformity which develops occasionally as a result of fractures in the region of the elbow or as a result of dislocation, especially in young subjects. The mode of production is regarded as of the same nature as in the case of torticullis. After the injury the related muscles show hæmorrhage into their substance and œdema, and these are due to injuries to the veins. There is considerable necrosis of the muscle and this is followed by overgrowth of fibrous tissue and contraction.

Myositis Ossificans Progressiva. In this affection there occurs a progressive ossification of various muscles in the body, and in some cases almost the whole skeleton has been immobilised by the newly formed bone. The affection starts in early life, usually in infancy, and the muscles first affected are those of the neck, back, and shoulders; the disease then extends to other muscles, those of mastication being not infrequently involved. The first indication of the disease is the formation of doughy and sometimes painful swellings in the muscles. The swellings then gradually subside, but areas of fibrosis are left and in these ossification takes place; in this way strands and plates of bone of an irregular form are produced in the muscles. The disease advances by a series of attacks rather than by steady progression, and the exacerbations are sometimes accompanied by fever. The condition is a rare one and nothing is known of its real etiology. It is a striking fact, however, that in more than half the cases microdactyly has been present, and sometimes there have been other congenital abnormalities. It is thus likely that in myositis ossificans there is a congenital tendency or disposition to bone formation. It affects specially the male sex. There is no evidence that the disease is hereditary.

Apart from the general form of ossifying myositis just described, local ossification in muscles is not rarely met with, usually produced by irritation or by slight contusion often repeated. A well-known example of this is the development of bone in the adductor muscles of the thighs in riders. A corresponding condition is met with in the deltoid of soldiers, produced by the shock of the rifle in firing. It may be noted in this connection that injury to the periosteum and surface of a bone, especially if attended by hæmorrhage, may be followed by a considerable amount of bone formation; sometimes, in fact, the result may simulate a new growth in its general characters.

Trichiniasis or Trichinosis. This affection is produced in the human subject usually by the ingestion of imperfectly cooked pork containing the embryos of the *Trichinella* or *Trichina spiralis*. It is rare in this country, but is not uncommon on the Continent, where it is met with sometimes in epidemic form. The acute symptoms of the disease, to be described below, are due to the passage of the embryos to the muscles from the intestine, within which they are discharged from the mature females. The following are the chief facts with regard to the parasite and its life history:

Trichinella or Trichina Spiralis. When a muscle infested by this organism, e.g. a portion of trichinous pork, is examined, whitish oval specks may be seen with the naked eye, and, on microscopic examination, it is found that these represent small oval cysts or capsules within which the embryonic trichinellæ lie coiled up, usually one, though occasionally more than one, in each cyst. The cyst wall is a somewhat homogeneous membrane, and at the poles there are often small globules of fat. A number of the cysts may be the seat of calcification, and when the parasites die, they also become calcified. When such muscle is eaten by another animal, the cyst walls become dissolved by the gastric juice and the embryos are set free. In the bowel they reach full sexual maturity, the males measuring about 1·5 mm. in length, the females 3–4 mm. After copulation the males die, whereas the impregnated females bore their way into the wall of the small intestine. The parasite is viviparous and the young trichinellæ escape into the surrounding tissues, and especially into the lymphatic vessels; when newly born, they measure about 90 μ in length, their thickness being rather less than the diameter of a red blood corpuscle. They then travel along the lymphatics to the thoracic duct and thus reach the circulating blood, by which they are distributed to various parts of the body. Settling especially in the capillaries of muscles, they then emigrate into the substance of the muscles. They have been found in numbers in the peritoneal cavity and other serous sacs, and from these also make their way directly into the muscles. A trichinella embryo pierces the sarcolemma of a muscle fibre and passes along it; it then becomes arrested, usually towards the extremity, and the sarcous substance in its vicinity is seen to become homogeneous in appearance and then to disintegrate. The parasite becomes coiled up and develops a capsule around it, as already described; the rudiments of alimentary and reproductive systems appear, but no further development takes place. The parasites are most numerous in the muscles of the abdominal and thoracic walls, the diaphragm, muscles of the pharynx and tongue, and oculo-motor muscles. Amongst the lower animals trichiniasis is commonest in the pig and rat, but it has been found by experiment that a large number of other animals are susceptible. The stages of development have been fully worked out, and it may be said that impregnation of the female occurs within two days after the parasites have been swallowed, the young embryos are fully developed in about a week, and begin to reach the muscles about the ninth day, becoming fully encysted about a week later. Fresh embryos, however, are produced and continue to pass to the muscles until the females have completely discharged their young, this process occupying a period of 5–7 weeks.

The SYMPTOMS which occur during the passage of the young parasites from the intestine to the muscle vary much in intensity according to the number of the parasites; sometimes they are slight, sometimes they are of a severe nature and occasionally are followed by a fatal result. When the infestation is a comparatively heavy one there are usually signs of intestinal irritation, diarrhœa, colicky pains, etc., and these are followed in a few days by tenderness and pains in the muscles, especially on movement; the muscles may become swollen and firmer in consistence. Respiration, mastication, phonation, etc., are attended with pain and difficulty. Œdema, especially of the face, is not uncommon at an early period; it may pass off and reappear at a later period. There are also symptoms of marked toxæmia, including pyrexia, and the disease may resemble typhoid fever in its general features and course. A fatal result is usually due to extensive involvement of the muscles of respiration, to which inflammatory conditions of the bronchi and lungs are often superadded.

During the symptoms of the infection, marked eosinophilia is present in the blood, but this gradually disappears when the parasites are completely encysted in the muscles.

Myopathy. Under this term there is included a group of obscure affections of muscles which, so far as is known, are not due to lesions in the motor neurons. The terms *muscular dystrophy* and *idiopathic muscular atrophy* are used in the same sense. Such affections usually appear in the early years of life and are apparently due to some congenital defect in the muscles. Not infrequently they occur amongst members of the same family and appear in successive generations; that is, they have familial and hereditary characters, although variations in these respects are met with amongst the different types of myopathy which have been distinguished. The affected muscles show gradual wasting with loss of power, and there is also weakness of the response to the galvanic and faradic currents, but without any reaction of degeneration. In most cases the muscular atrophy is indicated by decrease of the size of the muscles, but in one group it is accompanied by lipomatosis or accumulation of fat in the connective tissue, so that the size of the affected muscle becomes increased. To the latter type the term *pseudo-hypertrophic paralysis* has been applied.

Several types of myopathy without lipomatosis have been described according to the distribution of the lesions, but there appears to be no essential difference in the morbid change met with in the several varieties. In some cases, for example, the muscles of the shoulder girdle are especially affected, and in one type there is also an associated affection of the muscles in the face; in other cases there is a general wasting of muscles with loss of power throughout the body; or again, the muscles of the extremities may specially be the seat of the lesion. Pseudo-hypertrophic paralysis usually appears in childhood, though sometimes later; it has a markedly familial character and usually affects boys, though it is interesting to note that transmission to subsequent generations through females has sometimes been observed. In this condition some muscles become enlarged, especially the calf muscles, the glutei and some of the muscles of the shoulder girdle; whilst others undergo the ordinary atrophic changes. The enlargement of the calves is often a prominent feature, and the muscular weakness is in contrast to the apparent muscular development.

In all these types of myopathy the histological changes in the muscles appear to be of the same nature. When a section of affected muscle is examined some fibres are found to be larger than the normal, whilst most show various degrees of atrophy up to complete disappearance. The enlarged muscle fibres may show simply the appearance of hypertrophy and may be well striated, but not infrequently they show signs of degeneration, their transverse striation being lost and their aspect being homogeneous, granular, or vacuolated. In some of the larger fibres there may be proliferation of the sarcolemma cells, so that rows of nuclei are formed; and this may be followed by splitting up of a fibre into several small fibres. In an atrophic area the number of minute fibres is often very great, and we consider that there is no doubt that many are formed by the process described, whilst others are merely atrophied fibres. The minute fibres may be well striated or they may have a homogeneous appearance. In the pseudo-hypertrophic type there is, as we have said, an accumulation of adipose tissue between the affected fibres, and there is also a certain amount of thickening of the fibrous tissue (Fig. 536). Thickening of the walls of arteries is sometimes present as an associated condition, but there is no evidence that it is the cause of the atrophic change. The muscle spindles have usually been found normal even in the atrophic areas. Changes have been described in the end-plates and the terminations of the nerve fibres by some observers, but the view generally held is that myopathy represents a primary affection of the muscles.

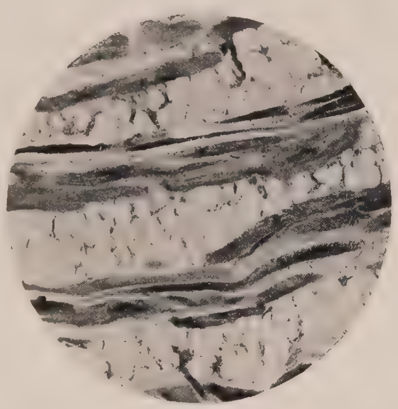
Fig. 536.—Section of Muscle in Pseudo-hypertrophic Paralysis, showing Infiltration of Fat Cells between Muscle Fibres. × 60.

Peroneal Atrophy (*Charcot-Marie-Tooth*). This affection has a relation to the myopathies so far as the conditions of its occurrence are concerned; it is of hereditary character, usually developing in the first decade of life, and boys are affected much more frequently than girls. Its pathology, however, is different, as the atrophic changes in the muscles are secondary to degeneration of the lower motor neurons. The atrophy, which is usually symmetrical, appears first in the peroneal muscles, the foot becoming dropped and inverted, and then spreads to the muscles of the calves. In addition to atrophy of the corresponding motor neurons in the cord, degenerative changes have been found in the posterior columns, in Clarke's column, and sometimes also in the pyramidal fibres.

Myotonia Congenita, or Thomsen's Disease. This is a rare affection in which peculiarities in the muscular contractions are associated with the structural changes in the muscle fibres. As in some myopathies, a distinct hereditary factor can usually be traced, and several members of a family are sometimes affected; it is commoner in the male than in the female sex. When a voluntary movement is performed by a patient suffering from the disease, the muscular contractions take place more slowly and last longer than in a normal individual; the movements of the body are thus altered in character. A similar prolongation of the stage of contraction is observed in response to mechanical or electrical stimulation, and usually the commencement of the contraction is delayed. Microscopic examination of the voluntary muscles has shown that their fibres are increased in size, striation is often poorly marked, and there may be some increase of the sarcolemma nuclei. No change of importance has been found in the nervous system. The disease is to be regarded as the result of some congenital defect in the muscles, though the symptoms may not develop for a considerable number of years after birth. Nothing definite, however, is known with regard to its true etiology. Sometimes myotony is associated with atrophy of parts of the muscles, the condition being then known as *myotonia atrophica.*

Myasthenia Gravis. This rare but very interesting affection is characterised, as the name indicates, by marked muscular weakness, which in certain muscles may amount to actual paralysis. This impairment of muscular power occurs generally, but is especially marked in the muscles of the face. Muscular contraction is found to be weak and of short duration when the muscles are stimulated by the galvanic or faradic current. The affection occurs in early adult life and is met with in the two sexes equally ; there is no evidence of its being hereditary. With regard to the nervous system, no change of importance in relation to the pathology of the disease has been discovered. On the other hand, in the muscles distinct lesions have been observed, though they are not special to the muscles but form part of a general condition. In the interstitial tissue of the muscles, especially round the blood vessels, areas of infiltrations of small cells are met with, these being chiefly lymphocytes and plasma cells ; such infiltrations are often spoken of as ‘ lymphorrhages.’ The muscle fibres in the vicinity usually appear healthy, though some of them may show signs of swelling and degeneration ; occasionally they are invaded by the small cells. True muscular atrophy, however, is rare. Similar infiltrations have been found in internal organs, for example, the liver and supra-renals. Hyperplasia, and sometimes actual tumour, of the thymus have been present in some cases, and congestive enlargement of the parathyroids has been described. In some instances the myasthenia has been associated with exophthalmic goitre. The nature of the disease is still obscure, but the facts indicate that it may be due to some disturbance of the endocrine glands. And the fact that the condition has been repeatedly found to improve during pregnancy is suggestive in this connection.

CHAPTER XIX

REPRODUCTIVE SYSTEM

MALE GENERATIVE SYSTEM

The diseases of the male genital tract comprise chiefly inflammations due to infections, tumours, and various congenital abnormalities, and, though of less frequent occurrence, correspond in a general way with those of the female tract. Another important subject is the relation of the genital system to endocrine secretion. The normal development of the various parts depends, of course, upon a healthy state of the testicles, or rather on the production in sufficient amount of the male sex hormone, which is formed by the interstitial cells of Leydig ; this hormone is allied structurally to oestrone (p. 870). Further, the formation of the hormone in its turn is now known to be influenced by the condition of the other endocrine glands. This subject, however, will be treated in a later chapter.

INFLAMMATORY CONDITIONS

Acute inflammations of the male genital tract are due to two main causes, namely : (*a*) gonorrhœa, and (*b*) septic infections, usually secondary to cystitis. Metastatic infection by the blood stream also may occur, but it is less common.

Gonorrhœal Infection. In gonorrhœa there is an acute catarrhal inflammation which ascends from the meatus of the urethra and is attended by inflammatory swelling of the sub-epithelial tissues. The discharge is at first thick and glairy, but soon becomes purulent, and in it gonococci, mainly intracellular in position, are usually to be found in considerable numbers. The disease, after running a course of several weeks, often subsides and a return to normal occurs, but not infrequently it passes into a chronic condition or ‘ gleet.’ Infection may spread to other parts from the urethra. This often occurs in the prostate, for example, and may be attended by a varying amount of acute inflammatory swelling, whilst in the chronic stage gonococci often persist in the tubules of the gland and maintain the infection. The organisms may also ascend by the vas deferens to the testicle and set up acute inflammation, which first affects the epididymis—*gonorrhœal epididymitis.* The inflammation is usually restricted to the epididymis, but in severer forms there may be some extension to the body of the testicle ; it is usually of an acute character, and not infrequently leads to local suppuration in the epididymis. At a later stage, when the condition subsides, fibrosis with obliteration of the tubules is a common result, and thus obstruction to the passage of the semen is produced. Occasionally both testicles are involved, and complete aspermia and sterility may be brought about ; the changes which follow castration, however, do not take place, as the internal secretion of the glands is still supplied. Infection of the bladder by gonococci with resulting cystitis occasionally occurs. Two other forms of serious complications are met with in later stages. On the one hand, there may be ulceration of the urethra, especially in its posterior part, and stricture often follows. This in its turn leads to dilatation and hypertrophy of the bladder ; secondary infection by other organisms and septic cystitis, etc., are common results. On the other hand, the organisms may be distributed by means of the blood stream and give rise to inflammations in other parts of the body. The commonest of these are in connection with the joints, sheaths of tendons, etc. (p. 843), but occasionally other conditions, such as pleurisy, endocarditis and even septicæmia (as shown by blood culture) are met with.

Orchitis. In addition to gonococci, the testicle may be infected by other organisms, usually of the coli group, in cases of cystitis. Here also the infection appears to be an ascending one by the vas deferens, and the epididymis is first involved, though there may be extension to the substance of the testicle. The inflammation may be attended by suppuration, and at a later date by fibrosis and obliteration of the tubules, just as in gonorrhœal cases.

Of infections by the blood stream, the commonest is that which occurs in mumps, this complication being comparatively common. The lesion is a diffuse inflammation of the testis itself, and never becomes suppurative. It may give rise, however, to a certain amount of fibrosis with atrophy of the substance of the testis. Metastatic inflammation may occur in some other fevers, e.g. in smallpox and in various septic conditions, the organisms in the latter being the ordinary pyococci, pneumococci, etc. The lesion may be suppurative or non-suppurative.

Chronic Orchitis. This may be the result of the acute conditions already described, or it may be of chronic nature throughout—*primary fibrosis* of the testicle, which may be localised or diffused. Such a lesion may be associated with gumma, and, as in other organs, fibrosis apart from gumma may be of syphilitic nature. In many instances the etiology of interstitial fibrosis is obscure.

Prostatitis. Acute inflammation of the prostate is usually produced by extension of organisms from the urethra, as has been described in the case of the epididymis, and the two commonest conditions in which this occurs are again gonorrhœa and septic cystitis. The gonococcus produces an acute catarrhal inflammation in the prostate with swelling of the surrounding tissue, and is attended by increased secretion. Gonorrhœal prostatitis not infrequently passes into a chronic condition and, as already stated, the organisms may persist for a long period of time in the tubules. In cases of septic cystitis acute inflammation of the prostate is often followed by suppuration, which may be in the form of multiple foci; or a large abscess may form and the prostate may be in great part destroyed. Similar inflammatory and suppurative conditions are met with also in the vesiculæ seminales in the conditions mentioned.

Chronic interstitial prostatitis or *prostatic fibrosis* is a condition in which there is a diffuse growth of connective tissue throughout the gland, leading to diminution in size. It may lead to the obstructive effects of a hypertrophied prostate. Its etiology is unknown but probably it is the result of a mild infection.

SPECIFIC INFLAMMATIONS

Tuberculosis. Tuberculosis of the *testicle* is comparatively common, and is usually of hæmatogenous origin, being secondary to a tuberculous lesion in some other part of the body; in some instances it results from the spread of bacilli along the vas deferens from the base of the bladder. In nearly all cases the epididymis is first affected. Tubercles form in some part and undergo caseation, and ultimately the tissue of the epididymis may be entirely destroyed. The epididymis becomes enlarged and dense, and forms a sausage-shaped structure attached to the testis (Fig. 537). On section, large caseous areas are seen and, not infrequently, parts have undergone softening. At a later period there may be extension to the tunica vaginalis, which may become obliterated by fibrous adhesions, or may be the seat of tubercles or of caseous inflammation; the disease then sometimes extends into the substance of the testis.

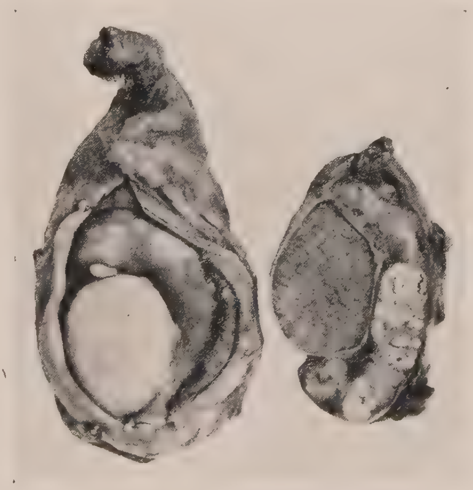

Fig. 537.—Tuberculosis of both Testes: in A, irregularly swollen Epididymis is seen above the Testis; in B, the caseation in the other Epididymis is shown on section.

In untreated cases there may be involvement of the skin, and ulceration with formation of a sinus may follow. The vas deferens usually becomes affected; on section the lumen may be seen to contain caseous pus or may be obliterated at parts. The disease ultimately reaches the vesiculæ seminales, and may involve also the prostate and the base of the bladder. As already mentioned, it occasionally spreads in the reverse direction, i.e. upwards from the bladder to the epididymis in cases of urinary tuberculosis. Primary tuberculosis of the body of the testis is of rare occurrence, but we have occasionally seen it in children.

Tuberculosis of the *prostate* is occasionally primary, but in the great majority of cases is the result of secondary infection, either by the vas deferens from the epididymis or from tuberculous disease of the bladder in urinary tuberculosis. It is usually of the caseating type and the gland may be largely destroyed. When septic cystitis is present, as is not infrequently the case in tuberculous disease, there may be also infection with pyogenic organisms, and suppuration in the gland may be superadded. Tuberculosis of the vesiculæ seminales is of common occurrence in the conditions mentioned, and the lesions are often of extensive nature. The vesicles become greatly enlarged and tense, and, on section, their substance may be found to be entirely replaced by caseous material which is usually softened in the central parts.

Syphilis. Apart from the primary sore, which has been already described (p. 102), the commonest site of a syphilitic lesion in the genital tract is the testicle, where it is not uncommon. The lesions are gumma or diffuse interstitial inflammation, and the two are often combined. Unlike tuberculosis, gumma starts almost invariably in the body of the testicle; and it may cause great general enlargement and induration. Extensive necrosis occurs, and the necrotic areas are often of irregular outline and form a contrast to the rest of the tissue (Fig. 538). Syphilitic orchitis may occur without gummatous change, and is characterised, as in other organs, by growth of cellular connective tissue which afterwards becomes fibrosed, whilst the tubules become atrophied and disappear. At first there may be a certain amount of enlargement, but later induration and contraction result. A diffuse interstitial orchitis has been described as occurring in the congenital form, but it is very rare.

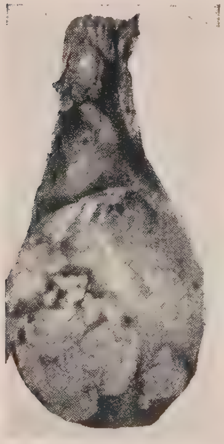

Fig. 538.—Gumma of Testis, showing large irregular Necrotic Areas. × ½.

Hypertrophy of the Prostate

This is a common condition after the age of about fifty, and great enlargement is sometimes met with. Both lobes of the gland may be uniformly enlarged, but often one more so than the other, and the surface may be comparatively uniform or may present some nodulations. Such enlargement leads to compression of the urethra, which is often changed into a vertical slit, and various bends may be produced when the enlargement is irregular. There may be also enlargement of what is called the third or middle lobe of the gland, which comes to form a rounded swelling, growing up at the inner end of the prostatic urethra, and may reach a large size (Fig. 539). This so-called lobe is hardly present normally as a distinct structure, but is represented by collections of glands under the prostatic urethra behind the verumontanum, and these undergo great enlargement. Enlargement of the middle lobe is usually associated with enlargement of the rest of the gland, but it may be proportionately much greater, and is often the chief cause of obstruction. A hypertrophied prostate varies in consistence, but is usually pretty firm; on section, it may have a fairly uniform appearance or adenomatous nodules may be present. The urethra is variously affected; it may be lengthened, compressed laterally, curved, etc., according to the character of the prostatic enlargement. The resulting obstruction is followed by the usual changes, hypertrophy of the bladder, dilatation of ureters and renal pelves, etc. Not infrequently a certain amount of fibrosis of the kidneys follows along with functional interference. The blood urea often rises and a state of chronic uræmia may result; a fall in the blood urea usually occurs after drainage of the bladder. Septic inflammation of the urinary tract is often superadded (p. 703).

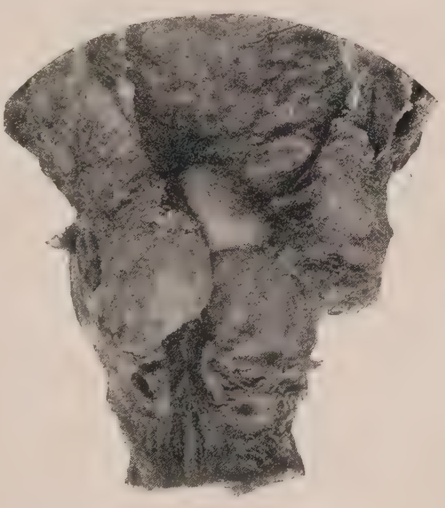

Fig. 539.—Hypertrophy of Prostate involving all three Lobes; the Bladder Wall above is hypertrophied and its Mucosa irregularly thickened.

Microscopically there is usually found increase both of the glandular elements and the stroma (Fig. 540). The former are arranged chiefly in acini lined by columnar cells, and not infrequently show small papilliform ingrowths into the spaces. Some of the acini are often dilated and occasionally small cysts are formed ; small concentric concretions or 'corpora amylacea' are of common occurrence. The stroma is usually a fibrocellular connective tissue, and contains a varying proportion of non-striped fibres. While the gland acini are usually lined by a definite epithelial layer, there may be found at places more active hyperplasia with the formation of masses of cells. Aberration in cell types may then appear and, in fact just as in the case of the mamma, all transitions to malignant growth may be followed. Enlarged prostate has been described as sometimes due to increase of muscle, but such a condition is certainly rare. The development of a carcinoma in a hypertrophied prostate is not uncommon.

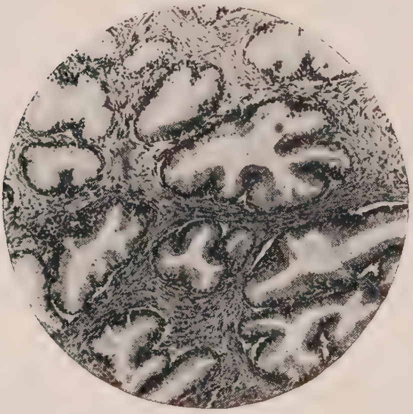

FIG. 540.—Section of hypertrophied Prostate, showing Hyperplasia of the Glandular Epithelium. × 60.

Nothing definite can be said with regard to the real cause of prostatic enlargement. Whilst the enlargement may follow chronic infections, there is in most cases no evidence of such a sequel of events, and we do not consider that the structural changes can be regarded as of inflammatory type. The frequent occurrence of the condition and its general course, at a certain time of life, points to some definite cause at work. In this connection it is interesting to note that the injection of œstrone and allied chemical compounds in male mice leads to prostatic enlargement along with other hyperplastic and metaplastic changes in the urinary tract (Burrows and Kennaway). There is also a certain resemblance of the histological changes to those met with in cystic hyperplasia of the mamma and, as in the latter, transitional stages to carcinoma may be found. On the whole it is likely that prostatic enlargement results from endocrine disturbance, but it is not possible to state how this arises and what its nature may be.

CYSTS

These occur mainly in connection with the testicle. The commonest is *hydrocele*, which is the result of distension of the tunica vaginalis with clear serous fluid. It may originate sometimes in connection with chronic inflammatory conditions of the testicle or with traumatism, but often it occurs apart from any such condition and the causation is obscure. Along with the accumulation of fluid there occurs a varying degree of thickening of the tunica, and sometimes this is of marked degree ; inflammatory change is sometimes superadded. Occasionally hæmorrhage into the sac occurs, usually as the result of some form of traumatism, and then the term ‘ hæmatocele ’ is applied. Clotting of the blood may take place, and the organisation which follows may lead to great thickening of the wall of the space. *Encysted hydrocele* or *hydrocele of the cord* is due to a distension with fluid of the non-obliterated remains of the spermatic funiculus or original communication between the tunica vaginalis and the peritoneum. Sometimes the funiculus is obliterated only at its lower end, and there is an elongated space containing fluid in communication with the peritoneal cavity. Cysts of the body of the testis are rare, but are not uncommon in connection with the *epididymis.* They are usually multiple and small, but occasionally a single cyst may reach a considerable size and displace the testicle. The contents of cysts in this position are usually a clear or turbid fluid, and not infrequently contain spermatozoa, often in a degenerated condition ; the cyst is then known as a *spermatocele.* Occasionally rupture into the tunica vaginalis may take place. Cysts of the epididymis are believed to arise by obstruction, especially of the vasa aberrantia, though some may be of congenital origin. A cyst may form also from dilatation of the hydatid of Morgagni.

TUMOURS

Tumours of all kinds are much less common than they are in the female genital tract. The following is a summary of the chief varieties :—

Penis. The commonest growth is squamous epithelioma, which usually originates from the glans or prepuce ; it presents the usual characters. Papilloma is often the result of chronic irritation, especially of gonorrhœal origin. The so-called gonorrhœal warts occur chiefly in connection with the mucous membrane of the prepuce and corona ; they may be multiple and often reach a considerable size.

Testicle. *Fibroma* and *leiomyoma* are occasionally met with, but as a whole simple growths are very rare.

The two most important tumours are (*a*) seminoma and (*b*) teratoma.

(*a*) *Seminoma.* This interesting malignant growth of the testicle is composed of spheroidal cells which form large masses with comparatively little stroma or which may have more of an alveolar arrangement (Fig. 541). The growth is vascular and areas of hæmorrhage and necrosis are common. Not infrequently it resembles a large round-cell sarcoma and was often described as such. It is now, however, generally considered to arise from the spermatoblasts and accordingly the above name is commonly applied. (Ewing, however, holds that it is of teratoid origin—‘ a one-sided development of a teratoma.’) The size of the cells varies in different specimens but usually they are relatively large; occasionally they have been described as small and resembling those of a lymphosarcoma. The cytoplasm of the cells tends to have a somewhat ill-defined margin unless properly fixed. A seminoma forms a large cellular mass, displacing the surviving parenchyma and distending the tunica, and grows along the spermatic cord. Metastases frequently occur and evidence of these after the primary growth has been removed may not appear for a considerable time.

Other forms of carcinoma and also sarcoma are of rare occurrence; they may arise in connection with a teratoma.

(*b*) The 'mixed tumours' of the testicle, which are not uncommon, are to be regarded as *teratomata*, usually of the solid type (p. 261).

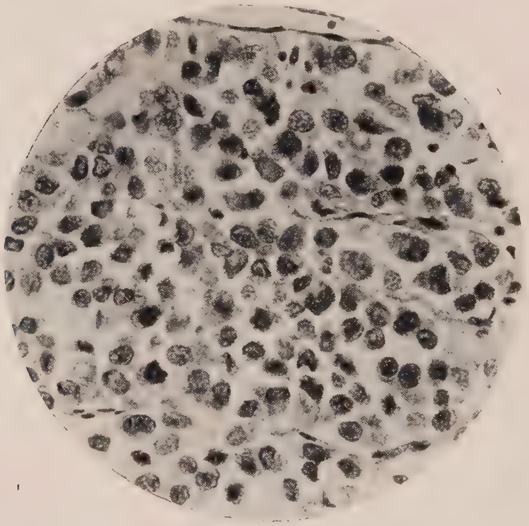

FIG. 541.—Seminoma of Testis, showing masses of round cells with very little stroma. × 300.

They may contain epithelium of various types, cartilage, bone, myxomatous tissue, striped and non-striped muscle, etc. All three germinal layers may be represented or one specially, the others being suppressed. Some of the epithelial structures may undergo dilatation and form cysts, but they usually do not reach a large size. Some growths are of less complicated structure and only some of the tissues mentioned are present, cartilage not infrequently predominating; all intermediate forms are met with. One form in which the constituents are fibrous tissue, cartilage and cysts lined by epithelium, is known amongst surgeons as 'fibro-cystic disease.' Though a teratoma is a congenital abnormality, it usually does not produce much enlargement and lead to a distinct tumour till the time of adult life or even later. Sometimes there is a history of a blow preceding the actual growth. Malignant growth frequently arises in connection with a teratoma and gives rise to metastases. The secondary growths may be carcinomatous, sarcomatous or of mixed type. Lastly, as in the case of teratomata elsewhere, a chorion-epithelioma with the usual characters may develop. It is a matter of much interest that in a case of chorion-epithelioma arising from a testicular teratoma the urine may give the Ascheim-Zondek reaction found in pregnancy (p. 720). Recent observations show that this reaction may be given by other testicular tumours such as adenocarcinoma, seminoma, etc., although the hormone concerned is present in very much smaller amount. Occasionally, though very rarely, a teratoma of the testicle may have the characters of the common ' desmoid cyst ' of the ovary.

It may be added that sarcoma of ordinary type and adenocarcinoma are occasionally met with, but they are rare.

PROSTATE. The most important tumour of the prostate is carcinoma, which is of not infrequent occurrence, sometimes as a sequel to prostatic hypertrophy. It usually produces enlargement of the gland, and for a time may be contained within the capsule, so that the condition may be supposed to be one merely of hypertrophy. Later, it grows through the capsule and invades the neighbouring tissues. The presence of malignant disease is often indicated at an operation by adhesions between the gland and its capsule. We may also note that when cancer of the scirrhous type is present, it may lead to general induration of the gland without enlargement, and we have seen cases where it was not possible to be certain of the condition till microscopic examination was made. The growth may be of the ordinary solid scirrhous type or less frequently may be an adenocarcinoma. An interesting point is that carcinoma of the prostate has a tendency to give rise to multiple secondary growths in the bones, and these may be attended by a great deal of bony thickening around them—*osteosclerosis* (p. 841). These osseous metastases may occur without the presence of secondary growths in the lungs or other organs.

Adenomatous nodules—single or multiple—occur in the prostate and all transitions to ordinary prostatic hypertrophy are met with. Cases of rhabdomyoma of the prostate also have been recorded. Sarcoma is a rare growth but is occasionally met with in children.

Tumours of the epididymis, seminal vesicles, and the various ducts of the genital tract, are all of great rarity.

CONGENITAL ABNORMALITIES

The term *hermaphroditism* is applied when the genital structures have the characters partly of the male and partly of the female type, and two forms, *true* and *false*, are to be distinguished. In true hermaphroditism, of which only a very few cases have been recorded, both testis and ovary are present. The exact conditions in the cases observed have varied—a testicle and ovary have been present on both sides ; or both on one side, with a testicle or ovary on the other ; or again, a testicle on one side and an ovary on the other. In false hermaphroditism or *pseudo-hermaphroditism*, where there is a blending of sexual characters, the sex, of course, depends on the presence of testicles or ovaries, and the condition is said to be of the masculine or feminine type accordingly ; in either case, the secondary sexual characters are usually those of the other sex. Pseudohermaphroditism is again distinguished as of internal or external type, according as the blending of the sexual characters affects the internal or the external structures. The commonest form of hermaphroditism is said to be of the masculine external type. In this condition, the scrotum is incompletely formed and remains split so as to resemble labia majora. The penis is rudimentary, and the urethra is usually not closed, while the testicles remain in the abdominal cavity or in the inguinal canals. In some forms of the feminine type, hyperplasia of the adrenal cortex has been observed (p. 963), but as a rule the causation is quite obscure.

Incomplete closure of the urethra is of not uncommon occurrence and the tube may remain open either on the dorsal aspect—*epispadias*, or on the ventral aspect—*hypospadias*. The latter is the more common and may be met with in varying degrees. Epispadias is often present in cases of extroversion of the bladder (p. 710).

Retention or *non-descent of the testicle* is frequently met with. The condition usually occurs on one side, though sometimes on both sides, and the retained testicle may be in the abdominal cavity or partly descended and in the inguinal canal. A retained testicle remains of a small size and in an undeveloped condition, spermatogenesis being absent, but the interstitial cells are not affected and appear relatively increased. As already mentioned, a malignant growth occasionally arises in connection with an undescended testicle in the inguinal canal.

FEMALE GENERATIVE SYSTEM

Scarcely any other region of the body is so frequently the seat of pathological changes as the female genital tract, and the lesions form a group of great importance and considerable complexity. We can deal only with the more important of these, and for details reference must be made to special books on the subject.[1] For convenience we shall consider the chief affections of the uterus, tubes, and ovaries together.

INFLAMMATORY CHANGES

Inflammations of the different parts of the female generative organs are of common occurrence, and may lead to divers serious results. In the great majority of cases the organisms enter by the uterine cavity, and thence infect other parts, though in certain instances, notably in tuberculosis, infection may occur by the blood stream.

(A) **Acute Endometritis.** The acute form of endometritis may be produced in various ways. In some cases there is no definite assignable cause, and the condition is attributed to ‘a chill,’ which may act by predisposing to infection. In other cases it is the result of infection during mechanical interference—the introduction of a sound, the internal application of medicaments, operation, etc. A not infrequent cause is gonorrhœa, which specially leads to a *cervical endometritis*, though the condition may spread to the body of the uterus and thence to the tubes. Gonorrhœal endometritis is often attended by a superficial interstitial metritis, and is apt to pass into a chronic state. There is also the very important group of infections of the body of the uterus which originate in connection with abortions and parturition, and which may lead to severe lesions and complications. Acute endometritis occurs occasionally in infective fevers—scarlet fever, smallpox, typhus, etc.

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[1] For further details the reader is referred to *Gynæcological* and *Obstetrical Pathology*, by R. T. Frank, 2nd edition, New York and London, 1931 ; a *Manual of Obstetrical and Gynæcological Pathology*, by J. H. Teacher, London, 1935 ; and *Gynæcological and Obstetrical Pathology*, by E. Novak, Philadelphia and London, 1940.

The changes in acute endometritis correspond with those seen in any inflammation of a mucous surface. There occur swelling and congestion of the mucosa, desquamation of superficial epithelium, sometimes with hæmorrhages, and increased secretion from the glands, that from the cervix being mucoid, that from the body more serous. Later the discharge becomes purulent. In severe cases, such as are met with after abortion or parturition and occasionally in fevers, the inflammation may be of the croupous type, there being a fibrinous exudate on the surface of the mucosa, attended with a certain amount of superficial necrosis which may be followed by ulceration. Acute endometritis may undergo resolution with a return to the normal, but frequently it passes into a chronic state. This is common in the gonorrhœal type.

Complications. Inflammatory conditions within the uterus are apt to extend and give rise to complications. As has been mentioned, metritis may occur, and there may be a spread by the lymphatics to the pelvic connective tissue, with diffuse inflammatory infiltration or *parametritis* as a result ; the inflammatory exudate may be serous, fibrinous, or even in some cases purulent. Thence the peritoneum may be infected. Extension of organisms may, moreover, take place along the Fallopian tubes, thus causing salpingitis and sometimes peritonitis and ovaritis. This latter mode of infection is common in gonorrhœa. It is, however, in connection with the *puerperal state* that the most serious complications are met with. Portions of retained placenta or decidua, and lacerations of the cervix, naturally give an opportunity for invasion by pathogenic organisms. In addition to the usual pyococci, various bacilli of the coli and proteus type and even gas-forming anærobes may be present. In some cases the changes are chiefly within the uterus, and the inflammatory process may be of severe phlegmonous character and may be accompanied by putrefaction of any retained material. There may thus be produced a state of ‘putrid intoxication.’ In another group of cases there is a spreading lymphangitis, which may be attended by suppurative foci at places, and by much inflammatory œdema ; naturally, spread to the peritoneum may occur and peritonitis follow. Or again, infection, especially at the placental site, may lead to septic thrombosis of the veins locally, and from these thrombosis may spread to the iliac veins with *plegmasia alba dolens* or 'white leg' as the result. Thrombi may undergo suppurative softening, and the setting free of septic emboli may cause a pyæmic condition with abscesses in the lungs, etc. More frequently, especially in cases of infection with haemolytic streptococci, an invasion of the blood by the organisms occurs, and the patient dies of septicæmia. In the less acute cases with spreading thrombosis anærobic streptococci may be concerned. The lesions described, which vary considerably and are combined in various ways, are attended by symptoms which are grouped together under the heading of 'puerperal fever.' It is hardly necessary to add that when recovery from the acute stages occurs, chronic effects of a permanent kind are often left—thickening of the pelvic connective tissue, peritoneal adhesions, chronic endometritis, etc.; and displacements of the uterus are a common result.

(B) **Chronic Endometritis.** In some cases this follows on an acute attack, whilst in many others it is of a chronic character from the onset. The lesion may be regarded as the result of infection of mild character and this usually arises in connection with pregnancy or is of gonorrhœal nature. It is apt to occur in connection with other morbid conditions, such as flexion or version, the presence of tumours, etc. It is not infrequently associated with sub-involution of the uterus after parturition and increased size of the uterine cavity. It must be recognised, however, that many cases of 'chronic endometritis' are not really of inflammatory nature, but are due to a disordered state of the mucosa brought about by endocrine disturbance. This is especially the case with the hypertrophic or hyperplastic variety (*vide infra*).

Two types of chronic endometritis are often described according to changes in the mucosa, viz. *atrophic* and *hypertrophic*. In the former there are thickening and contraction of the interstitial tissue along with atrophy of the glands. Where there has previously been an extensive destruction of the mucosa, the contraction of the fibrous tissue may lead to stenosis, or even partial obliteration of the cavity of the uterus; occasionally accumulation of pus, or *pyometra*, may result. Fibrosis of the endometrium is sometimes associated with, and apparently the result of, arteriosclerosis. It has now been established that the so-called hypertrophic form is not of inflammatory nature, and we shall accordingly consider it under a separate heading (p. 869).

Chronic Cervical Endometritis or Endocervicitis. This is a much commoner condition than the corresponding affection of the body of the uterus. It may result from gonorrhœa, there being a secondary infection by pyogenic organisms, but it most frequently results from injury during child-birth. Complete healing of lacerations may not take place and infection of the tissues by pyogenic organisms occurs through them. The condition is often of very chronic character and gives rise to a mucopurulent discharge or leucorrhœa. Changes in the surface epithelium and also obstruction of glands with formation of small cysts may follow; these may be briefly described.

Cervical Erosions. This term is applied to red raw-looking areas which occur on the vaginal portion of the cervix around the external *os uteri*; their surface is either somewhat granular or irregular, or else comparatively smooth. The earliest change is actual erosion with loss of the superficial squamous epithelium, but the bare surface is soon covered over by a new epithelial layer of the columnar type, and underneath it glandular structures appear. Later still in the process of healing, this may be replaced by squamous epithelium. The columnar epithelium is believed to be derived from the lining of the cervix or its glands. Erosions appear in most cases to be secondary to catarrh of the cervix. There is described, however, also a congenital variety, which is apparently the result of abnormality in the differentiation of the epithelium around the os uteri. A not uncommon result of catarrh of the cervix is the formation of cysts around the os, known as *ovula Nabothi.* They are of small size, rarely larger than a pea, and are due to obstruction of glands. They may be associated with erosions, and small papillomatous growths also are met with in like conditions.

The term *ectropion* is applied to an eversion or turning out of portion of the cervical mucosa towards the vagina. It is not infrequently the result of a fissure of the cervix caused by laceration at parturition. The everted mucosa is naturally exposed to bacterial invasion from the vagina and to irritation, and its epithelium may become changed to the squamous type.

Endometrial Hyperplasia. This is the pathological condition associated with a type of irregular uterine hæmorrhage, *metropathia hæmorrhagica.* The affection may be met with at any time in child-bearing life but its maximum incidence is about the age of forty. The endometrium is in a condition of hyperplasia and forms a thick, soft and vascular layer; its surface often shows elevations and polypoid excrescences. Its thickness in exceptional cases may exceed half-an-inch. The microscopic appearances vary, but often in the deeper parts there is a general hyperplasia of the uterine glands and at a higher level many of these show dilatation with tendency to cyst formation and epithelial ingrowths. Cyst formation is often a prominent feature (Fig. 542). In the superficial parts there are patches of degeneration and necrosis, along with capillary thrombosis and hæmorrhage, also the presence of polymorpho-nuclear leucocytes in relation to these. The interstitial tissue generally is cellular and varies in amount; it is vascular and there may be hæmorrhages and œdema, but there is no leucocytic emigration apart from the superficial tissues. At the junction of myometrium and endometrium a certain amount of adenomyosis is commonly present.

As has been said, it is now recognised that these changes in the endometrium are not of inflammatory nature but are the result of ovarian dysfunction. The changes found in the ovaries vary, but usually a single follicular cyst or several cysts are present in one or both ovaries, and a striking fact is that, as a rule, no corpus luteum is present. It would appear that the essential factor is the absence of ovulation and the series of changes seems capable of a theoretical explanation in view of what is known as to the ovarian hormones. The ovarian follicle forms a hormone called *folliculin* or *œstrone* which stimulates the reparative changes in the endometrium following menstruation up to the time of ovulation (Fig. 543). The corpus luteum which then begins to form, produces another hormone, *progestin* or *progesterone*, which leads to further endometrial changes culminating in menstruation. These changes consist in enlargement and tortuosity of the glands with increased secretory activity (Fig. 544); there is also formation of decidual cells in the superficial part of the endometrium. Finally disintegration, starting in the latter region, occurs at the time of menstruation. Progestin also inhibits ovulation, as seen in pregnancy when the corpus luteum persists and enlarges. If ovulation does not occur the reparative changes due to folliculin persist in excess, as there is no corpus luteum formed and no progestin to complete the cycle by leading to disintegrative changes in the endometrium. The hyperplastic condition of the endometrium may thus be taken as the result of uninterrupted action of œstrone. In this connection it is a fact of importance that the changes in the

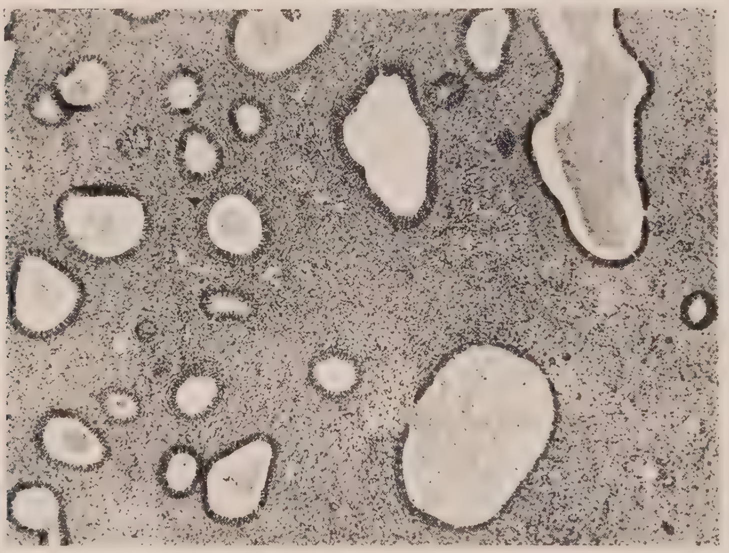

FIG. 542.—Section of Endometrium from a case of Metropathia Hæmorrhagica, showing dilatation of glands and early Cyst formation. (A. C. L.) × 40.

endometrium described are present also in granulosa-cell tumour of the ovaries, which produces œstrone in excess. In fact, when the endometrial lesion with bleeding is met with after the menopause there is a strong probability that the case is one of this tumour.

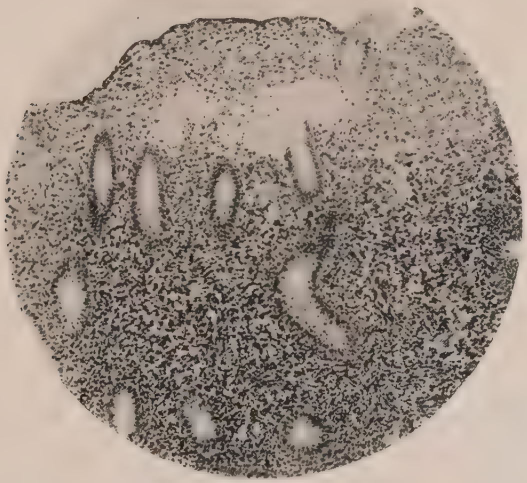

FIG. 543.—Section of Curetting, showing ordinary reparative or œstrone phase of Cycle. (A. C. L.) × 75.

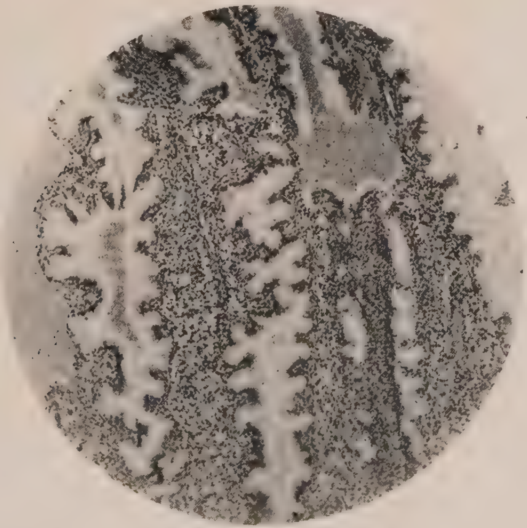

FIG. 544.—Section of Curetting, showing secretory or lutein phase of cycle. (J. F. Heggie.) × 75.

Another condition of obscure nature is known as *membranous dysmenorrhœa.* As indicated by the name, menstruation is attended by pain, and this is followed by the passing of membrane-like material in shreds or as a partial cast of the uterus. The membrane consists of the superficial part of the uterine mucosa, the interstitial cells of which are usually considerably swollen ; sometimes a considerable amount of fibrin is present. It is clear that the normal piecemeal disintegration of the superficial part of the mucosa, which occurs at menstruation, does not take place and that the tissue separates as a layer. But, although various theories have been put forward, nothing definite is known as to the cause of this abnormality.

Salpingitis. In the great majority of cases infection of the tubes is of the ascending type, and takes place by the extension of organisms from the uterine cavity in cases of endometritis, especially those of puerperal or gonorrhœal origin. In the small proportion of cases of the descending type, the organisms gain entrance from the abdominal cavity in appendicitis, peritonitis, etc. The common result is an acute catarrhal inflammation, which is attended by desquamation of epithelium and abundant leucocytic infiltration, so that the contents usually come to have a purulent character. Less frequently and in cases of severe type, there may be fibrinous exudation within the tubes, attended by superficial necrosis of mucosa. Inflammation extends usually to the serous surface and accordingly adhesions form, common results being fusion of the distal end with the ovary, and closure of the ostium. Progressive accumulation of pus within the tube is common, and the latter may undergo great dilatation resulting in a spindle- or sausage-shaped structure, which is often bent on itself and variously altered by adhesions—the condition of *pyosalpinx.* Later, the pus may become inspissated and the seat of calcareous deposit, while the wall may undergo great thickening ; the appearance may simulate that in tuberculosis. The organisms found in the pus are mainly gonococci and the ordinary pyococci, but in a pretty large proportion of chronic cases the organisms have disappeared and the pus has become sterile. When the latter condition is present there is a strong probability that the infection has been gonococcal. In gonorrhœal cases, a large number of plasma cells

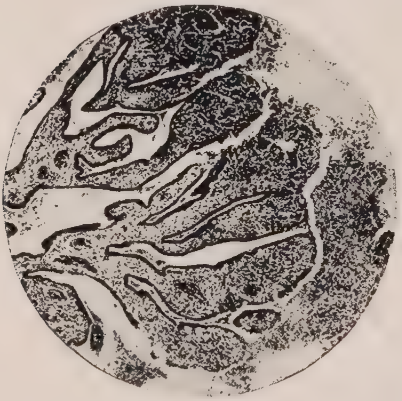

FIG. 545.—Chronic Salpingitis.

Note that the superficial parts of the folds (to the right) have lost their epithelium ; they are the seat of cellular proliferation and are becoming fused together. × 45.

may be present with polymorpho-nuclear leucocytes, both in the pus and in the interstitial tissue ; and this change is by some regarded as characteristic of the condition.

Salpingitis may pass into a chronic state without the occurrence of suppuration. The superficial folds of the mucosa lose their epithelium and grow together so that a reticulated appearance is seen on section ; thus numerous pockets and depressions are formed which are believed to play a part in leading to extra-uterine pregnancy. Adhesions also may form around the tube and local obliterations of the lumen may occur ; clear serous fluid may accumulate within the tube, leading to the condition of *hydrosalpinx.* In its production closure of the ostium or abdominal end is the important factor, as the uterine end so easily becomes blocked simply by inflammatory swelling. The fluid in a hydrosalpinx has accordingly sometimes been discharged by the uterus, this being followed by re-accumulation. Hæmorrhage may take place into a hydrosalpinx and thus *hœmatosalpinx* results. The blood usually remains fluid but becomes brownish in colour. This bleeding is supposed to occur especially from the congestion at the time of menstruation, though mechanical venous obstruction from twisting may play a part.

Ovaritis or Oophoritis. Acute inflammation of the ovaries is most frequently the result of secondary infection from the Fallopian tube by gonococci and the pyogenic organisms (p. 872). The inflamed end of the tube readily becomes adherent to the ovary, and thus organisms spread into the substance of the latter. Infection may occur also from the peritoneal cavity in cases of peritonitis due to appendicitis and other conditions. Ovaritis may be followed by suppuration either of a diffuse or localized character. Occasionally the whole substance of an ovary may be destroyed by suppuration, and the abscess may reach a large size. Naturally, such conditions are apt to be attended by at least local peritonitis. While suppuration is due chiefly to the ordinary pyogenic organisms, it may be caused also by gonococci, as in the case of the tubes.

Regarding *chronic ovaritis,* it is hardly possible to say much of a definite character, though the condition is often diagnosed clinically. It may certainly supervene on an acute inflammation, septic or gonorrhœal in origin. It is usually attended by chronic peritonitis, which is believed to interfere with the bursting of Graafian follicles and thus lead to the formation of follicular cysts. Cyst formation in general cannot, however, be ascribed to this cause. It must be recognised, however, that the interstitial fibrosis and scarring present in adult ovaries, represent most frequently simply the reactive changes set up around corpora lutea.

CHRONIC SPECIFIC INFLAMMATIONS

Tuberculosis. Tuberculosis of the female generative organs usually starts as a hæmatogenous infection of a *Fallopian tube*, secondary to some tuberculous lesion elsewhere; in this respect the tube occupies a position corresponding to the epididymis in the male. The tube may become infected also through the ostium in tuberculosis of the peritoneum, though spread in the reverse direction is commoner. The tubercle bacilli give rise to tubercles in the interstitial tissue of the tubal mucosa, and these soon lead to ulceration and destructive change, so that the lumen becomes filled with caseous material, while the wall is greatly thickened. Softening and accumulation of the caseous material often follow, and when the lumen is closed at the ends, the tube becomes greatly distended and filled with a caseous pus—the condition of *tuberculous pyosalpinx* (Fig. 546). Both tubes may be affected in this way; adhesions form and the tubes may be variously bent or twisted. The tuberculous infection may pass by the ostium to the peritoneum, but it may extend also through the wall of the tube, the surface of which may be beset with tubercles. In rare instances tuberculous salpingitis is due in young children to a direct spread of infection from the vagina (Blacklock).

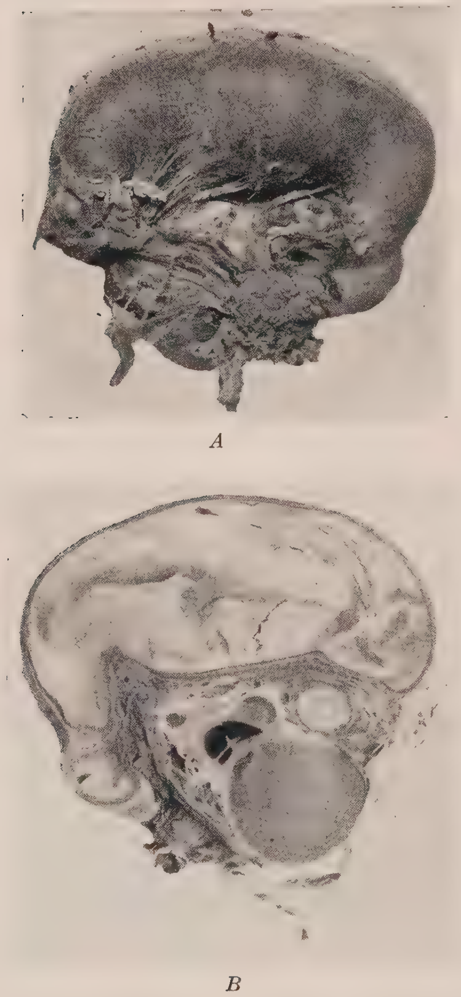

FIG. 546.—Tuberculous Pyosalpinx. (*A*) Surface view of tube, showing tubercles on serous surface. (*B*) View of section: above, a large caseous collection in the tube is seen; below, the ovary containing cysts. $\times \frac{2}{3}$.

Tuberculosis of the *uterus* is usually due to a descending infection from a tube, and is a not uncommon complication. Hæmatogenous infection occurs in acute miliary tuberculosis and minute tubercles may be present in the mucosa, even at an early period of life. Primary uterine tuberculosis is exceedingly rare, but the possibility of infection from a male suffering from genital tuberculosis must be admitted. In the common type of infection, secondary to tuberculosis of the tubes, the bacilli settle in the tissue of the mucosa, giving rise to tubercles which are often difficult to distinguish with the naked eye. A condition of *caseating endometritis* may follow. Occasionally obstruction of the lumen may occur, and an accumulation of caseous pus may then form. Rarely infection may spread from the uterus to the vagina, and ulcers may be produced in its wall. Tuberculosis of the cervix, which is much rarer than that of the body, may be attended by papillary excrescences.

Tuberculosis of the *ovaries* is relatively uncommon. Infection is usually secondary to tuberculosis of the tube and adhesions are often present ; less frequently infection occurs from tubercle of the peritoneum. Infection from the blood stream is exceptional. The lesion may be in the form of minute tubercles in the ovarian stroma, often in relation to the follicles, but distinct caseous nodules may be formed. In advanced cases the substance of the ovary may be destroyed and changed into a caseous mass, which is sometimes as large as a hen's egg.

Syphilis. The primary chancre occurs on the cervix uteri in a small proportion of cases, and during the secondary stage mucous patches and papular eruption on the vaginal portion may be met with. But apart from these, syphilitic lesions are not common and are somewhat ill-defined in their characters. Gummata have been described in various parts of the female genital tract, but are of rare occurrence. No doubt chronic interstitial inflammation takes place here as the result of syphilis, as it does in other organs, but without further evidence there is no means by which its syphilitic origin can be definitely recognised.

Actinomycosis. A few cases of this disease in the female genital tract have been recorded. The lesions are of the usual suppurative character.

TUMOURS

1. UTERUS

Tumours of the uterus, both simple and malignant, are of frequent occurrence and their characters constitute a subject of great importance. Of the simple growths, myoma, adenomyoma and the ' mucous polypus ' are most frequently met with, while carcinoma is the commonest malignant growth.

Simple Tumours. *Myoma* (Leiomyoma). This tumour forms a circumscribed growth of non-striped muscle along with supporting connective tissue, which may be abundant—it is thus often called a fibromyoma or a 'fibroid.' Uterine myomata are the commonest of all tumours met with in the body, being said to occur in more than 15 per cent. of women over 55, though in a considerable proportion of cases they do not reach a great size. The growths may be single or multiple, and in the latter case one is often much larger than the others. A myoma usually starts in the substance of the wall—it is then described as *interstitial* or *intramural.* But as enlargement takes place it expands in one of two directions, viz. into the cavity of the uterus—*submucous* type, or upwards under the peritoneum—*subperitoneal* type; or the growth may be of either of these types from the outset. A submucous myoma expands the uterine cavity, and may project through the os as a pedunculated mass (Fig. 547); occasionally it becomes expelled by the hypertrophied uterus. The growth tends to become ulcerated and the seat of septic infection; severe hæmorrhage is a common result, and if the tumour is not removed marked anæmia and cachexia may follow. A subperitoneal myoma passes upwards as it grows, and often comes to have a distinct neck or pedicle. It may reach a great size, sometimes weighing twenty or more pounds, and may cause great abdominal swelling. Also, a superficial myoma may pass between, and open out, the layers of the broad ligament.

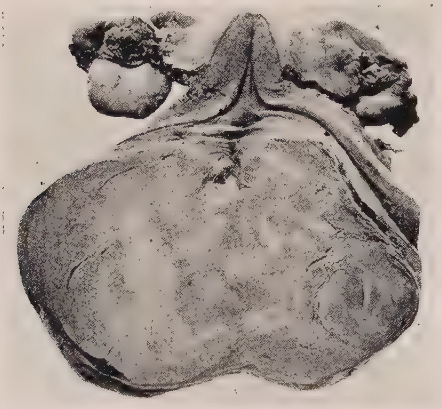

FIG. 547.—Large submucous Myoma of Uterus projecting through the Cervix; the Ovaries and Tubes are seen above.

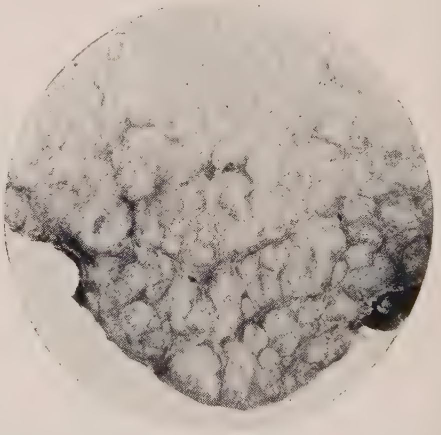

FIG. 548.—Portion of Myoma of the Uterus of conglomerate type, showing multiple foci of whorled arrangement.

A myoma is usually of firm and somewhat elastic consistence, with regular and well-defined outline; on section it is, as a rule, paler than the uterine wall and shows a peculiar concentric or whorled marking produced by the bundles of muscle fibres (Fig. 116). Occasionally the growth is composed of a number of foci and has a nodular outline—conglomerate type (Fig. 548). The microscopic characters have already been described. Sometimes a myoma becomes soft in consistence, owing to marked œdema, which is attended by a disappearance of the collagen fibres and of the muscle cells; or it may become myxomatous in parts (Fig. 549). These changes may become so pronounced that the tumour acquires a fluctuating character and clinically may simulate an ovarian cyst. The term 'cystic myoma' is sometimes applied to such a condition. Necrosis also may take place from thrombosis of vessels or from twisting of the pedicle, and softening of the tissue may follow; this may be accompanied by hæmorrhage into its substance—*red softening*. This change, the causation of which is often obscure, is commoner when pregnancy is associated with the tumour. At the menopause, uterine myomata usually cease to grow, and undergo a process of fibroid atrophy, so that considerable diminution in size results. The muscle cells atrophy and many may disappear, while the stroma becomes increased and hyaline (Fig. 550). Deposition of lime salts often occurs in the hyaline stroma and ultimately the tumour may be changed into a hard stony mass or 'womb-stone.' Even in a calcified myoma, when sawn through, the characteristic concentric markings may be distinguished. Although, as has been said, a myoma is usually less vascular than the uterine wall, in some examples a marked development of wide vessels occurs—*teleangiectatic*-form; and in others again, though more rarely, wide lymphatic spaces are formed. Occasionally sarcomatous change may arise in connection

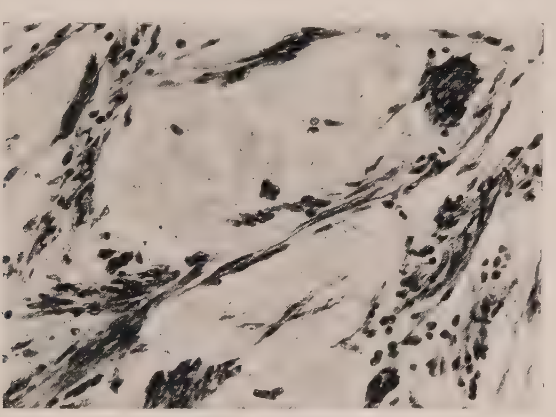

Fig. 549.—Myoma of Uterus undergoing mucoid change.
Note the clear material accumulating between the muscle cells. × 250.

with a myoma, and secondary growths may follow. Sometimes the origin of the cells of a sarcoma may be traced to the muscle cells, the tumour then being really a myosarcoma. The development of true sarcoma in connection with a myoma is, however, comparatively rare.

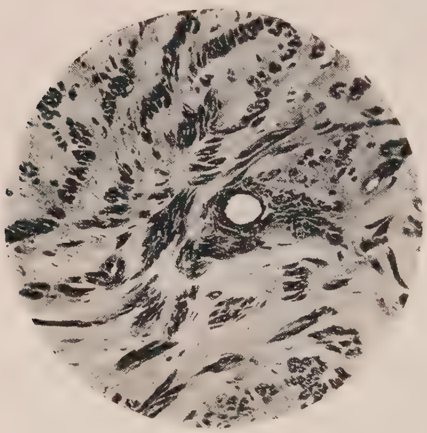

FIG. 550.—Myoma of Uterus undergoing fibrous change.

Note the large amount of hyaline connective tissue; the muscle cells appear dark. (G. H. W.) × 60.

Adenomyoma or *endometrioma*. This is a tumour in which there is associated growth of glandular tissue, stroma and non-striped muscle.

Within the uterus it is met with as two types, a diffuse and a more circumscribed. The *diffuse form* occurs chiefly in the inner part of the muscular tissue of the uterus, sometimes in one part, sometimes all round the cavity, the uterus being enlarged. The growth presents a somewhat nodular appearance with whorling as in a myoma, and in the muscular masses there may be small translucent areas and spaces which represent the glandular tissue. The outer part of the uterine wall is usually unaffected, and the line of the demarcation is not so sharp as in the case of an ordinary myoma. In the *circumscribed form* nodular masses of growth occur, which are usually multiple, and they come to form submucous or subperitoneal projections. The latter may reach a very large size and often are the seat of cysts with altered blood in the contents. The diffuse form is the commoner and has been called an 'adenomyosis,' though the condition appears to be of the same nature as the tumour masses. On microscopic examination, the glandular tissue is seen to be composed of branching slits with tubular and acinous structures, lined with columnar epithelium, and usually surrounded by a comparatively cellular tissue like that of the uterine mucosa (Fig. 551).

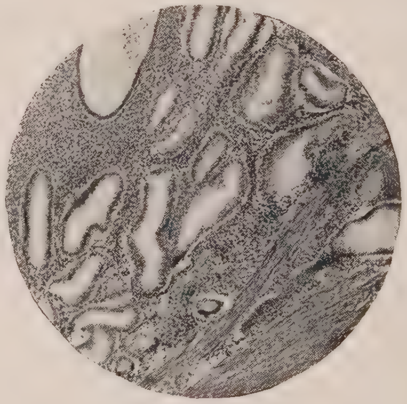

FIG. 551.—Adenomyoma of Uterus, showing acini with cellular stroma; muscle is seen at lower part. × 45.

But it may be regarded as established that the glandular tissue represents prolongations of the uterine mucosa, which grow in association with the myomatous tissue. The continuity of the glandular tissue with the lining epithelium of the uterus has been established by means of serial sections. The tumour is accordingly now often known as an *endometrioma*.

Bleeding sometimes occurs into the glandular spaces of an adenomyoma, and this is usually attributed to congestion of the glandular tissue during menstruation, just as in the interior of the uterus. The usual alterations may occur in the blood in the glandular spaces. Further, during pregnancy decidual cells have been observed to have formed from the included interstitial tissue round the acini.

Endometriosis. Growths of tissue resembling endometrium are met with outside the uterus and the term ‘ endometriosis ’ has been applied to such conditions. In the ovaries there occur cysts containing tarry or chocolate material, and in the lining of these a tissue-like endometrium may be present; the altered blood is the result of hæmorrhage during menstruation (p. 885). Endometriosis is found at various other places—on the peritoneal surface in the lower part of the abdomen, on the appendix and intestines, at the umbilicus, etc. It has been also observed on the outer aspect of the uterus extending inwards, in the recto-vaginal septum, in the inguinal canal, in laparotomy wounds, etc. The condition is indicated at an early stage by the occurrence of reddish or purplish patches, and in these there is a glandular structure accompanied by a stroma like that of the uterus. In most of the situations mentioned bleeding into the lesions has been observed to occur during menstruation and in some instances the formation of decidual cells has occurred during pregnancy. Endometriosis is met with only in the female sex after puberty, and it is agreed that the epithelium in it corresponds in all details with that of the endometrium. There has been much discussion as to the origin of endometriosis. One view is that the condition is due to transplants of small portions of uterine epithelium shed during menstruation (Sampson); such epithelium may stimulate the production of a stroma like that of the endometrium and it is unnecessary to suppose transplantation of stroma also. Such portions of endometrium have been found within the Fallopian tube, and it has been observed that blood sometimes escapes from the peritoneal extremity at the menstrual period. Peritoneal endometriosis is often associated with tarry cysts in the ovary, and it is believed that one of these may rupture and endometrial tissue may be spilled over the peritoneum. The other view is that endometriosis represents the result of metaplasia of the serosa of the peritoneum; it is widely held in Germany. The former view seems to us to have more in support of it, but there are various points still obscure.

Uterine Polypus. This, the commonest simple tumour of epithelial origin, may be regarded as a local outgrowth of the mucosa—often called a *mucous polypus.* Tumours of this nature grow either from the body or the cervix. In the former situation they are blunt or rounded projections, though sometimes pedunculated ; in the latter, they are often pear-shaped and project through the os uteri. The surface is usually relatively smooth, sometimes it is papillomatous, and sometimes cysts are present. Their size is usually comparatively small, rarely exceeding that of a walnut, and they may be either single or multiple. They may give rise to bleeding, or become the seat of septic infection which may extend to the uterine mucosa ; occasionally they become necrotic. A polypus consists of a vascular core or basis covered by a mucous membrane with glands which correspond to those of the corpus or cervix, though they are more irregular in their arrangement and often contain retained secretion. Sometimes the glands are specially developed in relation to stroma, so that an adenomatous type results and we may speak of a pedunculated adenoma. The connective tissue core may be cellular and vascular, or relatively fibrous. A cervical polypus may be covered in whole or in part by stratified squamous epithelium. Polypi may develop in association with inflammatory conditions or with hyperplasia of the mucosa, but are met with apart from any such conditions.

Malignant Tumours. *Carcinoma* of the uterus is a growth of frequent occurrence and causes widespread destructive changes. Two forms are to be distinguished according to the site of origin ; namely, *cancer of the cervix*, which may originate from the epithelium of the vaginal portion or from that of the cervical canal, and *cancer of the body.*

Cervical carcinoma is much the commoner, and is usually related to old lacerations, erosions, etc. For this reason, it is met with chiefly in women who have borne children, especially those who have passed through several pregnancies. Another point of difference is that it occurs at an earlier age than cancer of the body. While the incidence of cervical cancer is highest in the decade 45–55, more than a quarter of the cases are met with in the previous decade (Wilson). The growth presents the ordinary characters of a superficial carcinoma, starting usually as an irregular induration which undergoes ulceration (Fig. 552), sometimes as a sort of cauliflower excrescence. There is the usual infiltrative spread, ulcerative destruction is often a prominent feature, and the cervix may gradually become eaten away. Lymphatic invasion usually occurs at an early period and the parametrium may become infiltrated ; here also ulceration of the growth may take place and sometimes a fistulous opening forms into the bladder, which results in septic infection of the latter. The lower ends of the ureters may be involved, and partial or complete obstruction may ensue. The regional lymphatic glands are involved at an early date, while later the peritoneum may become infected. Metastases may occur in other viscera, liver, lungs, etc., but they are relatively uncommon until the local disease is well advanced. Cervical cancer is thus a growth which leads to early lymphatic invasion and causes extensive destructive changes locally. Histologically, its origin can be traced in most cases to the stratified epithelium of the vaginal portion. The growth is usually composed of solid and broad masses of infiltrating epithelial cells without formation of cell-nests (Fig. 553). Sometimes, however, typical cell-nests are present. The cells may show considerable aberrations in form and in nuclear character. In a certain proportion of cases of cervical carcinoma, the growth has the structure of an adenocarcinoma, this being especially the form when the origin has been from the glands of the cervical canal or from a cervical erosion where metaplasia of the covering epithelium has occurred.

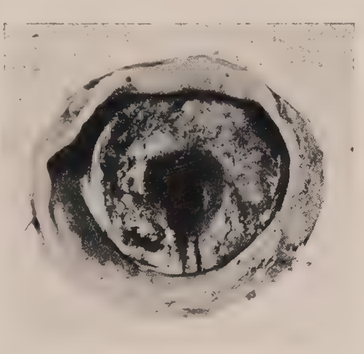

Fig. 552.—Carcinoma of Cervix Uteri in process of Ulceration. × ¾.

The common epidermoid type of carcinoma of the cervix is relatively sensitive to radiation and a considerable amount of success has been attained by such treatment. In accordance with the general law, the sensitiveness varies according to the degree of de-differentiation of the cells. The most anaplastic types of growth are the most

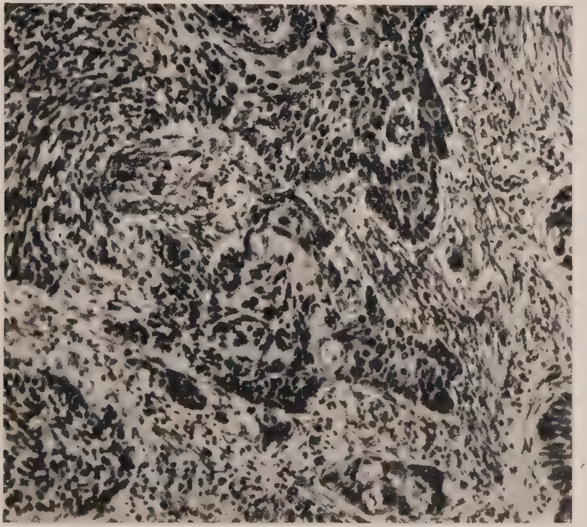

Fig. 553.—Carcinoma of Cervix Uteri, showing infiltrating masses of epithelial cells without formation of cell nests. × 150.

sensitive, those with well marked cell-nest formation the most resistant. Fig. 553 is an illustration of a growth occupying an intermediate position.

Carcinoma of the body of the uterus is much less common than the cervical variety. Statistics vary, but the relative frequency of the two forms may be stated to be about 1 : 20. Cancer of the body occurs at a later period of life, being very rarely met with before the age of 45, and there appears to be no relation to pregnancy. It is a common cause of uterine bleeding after the menopause. The growth is at first localised and appears as an irregular nodular thickening, or it may form masses of somewhat soft consistence projecting into the uterine cavity (Fig. 554). Not infrequently it extends over the lining of the uterus in a diffuse manner, though rarely passing into the cervix, and the inner part of the muscular wall is gradually destroyed. Lymphatic invasion occurs here also, but at a somewhat later period, as a rule, than in cervical cancer, and thus the prognosis in operative removal of the uterus is more hopeful. In the great majority of cases the growth is an adenocarcinoma, the epithelial cells being of a columnar type with atypical gland-like arrangement (Fig. 555); though in parts the epithelium may grow in solid strands. This type of cancer is more radio-resistant than the common type of carcinoma of the cervix. Cases are sometimes met with in which the structure of epithelioma with cell-nests is present, and such a condition has been ascribed to a previous metaplasia of the uterina mucosa.

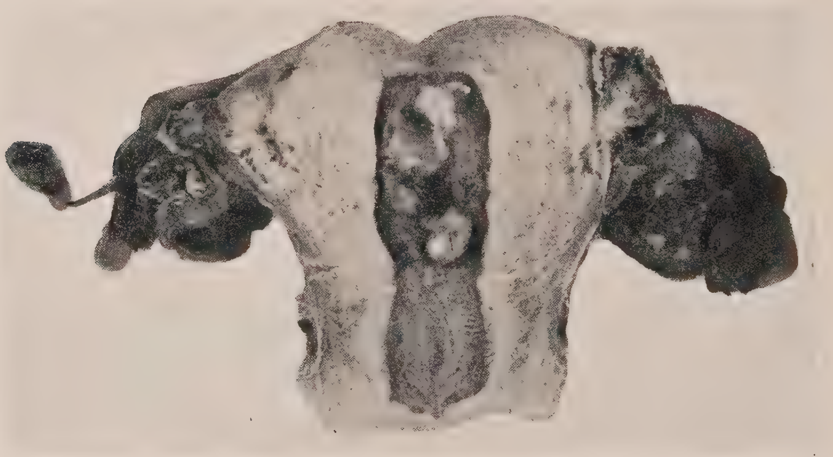

Fig. 554.—Carcinoma of Body of Uterus.

Note the irregular and ulcerating mass occupying the cavity of the body. × ¾.

Sarcoma of the uterus, though much less common than carcinoma, is by no means rare. It may originate in the mucosa and may form a large cellular mass, or it may grow more diffusely in the mucosa and cause destruction of the glands. In other cases it starts in the muscular wall, and in a certain proportion of these in connection with a myoma. Sometimes the origin of the growth can be traced to the muscle cells, in which case the growth is to be regarded as a myosarcoma. Uterine sarcoma is usually of the spindle-cell type, and this is the rule when it originates from a myoma, but the round-cell and mixed-cell varieties are met with. Angiosarcoma and chondrosarcoma are occasionally observed, the origin of the latter being unknown; and rhabdomyosarcoma also may be mentioned as a growth of very rare occurrence.

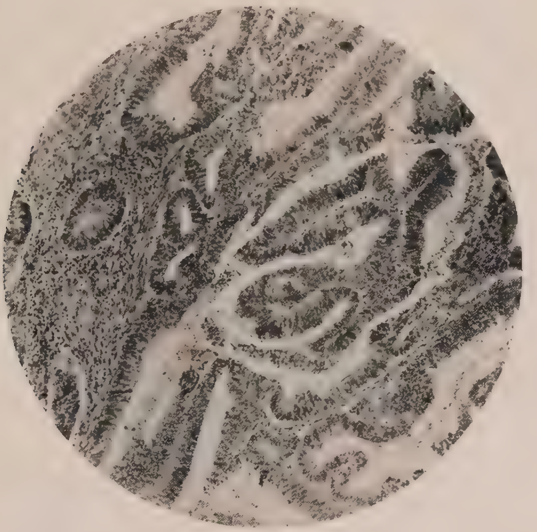

FIG. 555.—Adenocarcinoma of body of uterus, showing papilliform type of growth and also infiltration. (J. F. H.) × 75.

Chorion-epithelioma is described below (p. 896).

2. The Fallopian Tubes

Simple tumours—fibroma, myoma, adenoma—and small cysts sometimes occur in connection with the tubes, and malignant growths, both carcinoma and sarcoma, are occasionally met with; also cases of chorion-epithelioma as a sequel to tubal pregnancy have been recorded. All forms of growth, however, are relatively rare.

3. The Ovaries

The tumours of the ovaries are of considerable variety and some of them present features of special interest and importance. Both solid and cystic types are met with, the latter occurring much more frequently.

Simple Tumours. Of the solid simple tumours of the ovary the fibroma is the commonest. It is usually comparatively small, but sometimes reaches a large size, and transitions to sarcoma are met with. *Adenomyoma*, with formation of cysts and hæmorrhage into them, is described below (p. 885).

Cysts and Cystic Tumours. Cysts of the ovaries form an important group of abnormalities, and of these some represent simple exudation cysts derived from follicles or other structures, whilst others have the characters of tumours. We shall give the main features of the different types.

Follicular cysts are formed by the dilatation of Graafian follicles, though sometimes from corpora lutea—*true follicular cysts* and *corpus luteum cysts*, respectively. The former are usually multiple, and the surface of the ovaries may be beset with them. As a rule they are small, but occasionally a cyst may reach the size of a small orange ; they are generally present in both ovaries and may lead to atrophy of the ovarian substance. They are unilocular, but adjacent cysts may become confluent ; they have ordinarily clear serous contents, though sometimes recent or altered blood may be present. Occasionally considerable hæmorrhage takes place into a large cyst, forming a hæmatoma, and this in its turn may burst into the peritoneal cavity. Follicular cysts have a smooth wall which is lined by a single layer of cubical or columnar epithelium ; sometimes, however, the epithelial lining may be lost. In the smaller cysts ova may be present. The *corpus luteum cysts* are formed by exudation of fluid into corpora lutea, and their characters vary according to the stage of formation of the latter. The wall is often fibrous or hyaline without distinct epithelial lining, and lutein cells derived from the membrana granulosa may be present. Sometimes these cells are abundant and form a yellowish layer visible to the naked eye, and usually thicker at one side ; the term *lutein cyst* is then applied. The lutein cells are of comparatively large size, rounded or polyhedral in form, and contain abundant fatty material and also a yellowish pigment. They may form a broad zone which is surrounded and partly invaded by connective tissue. It may be added that lutein cells may be present in considerable number also in true follicular cysts, and in this case they are derived from the theca interna, not from the membrana granulosa—*theca-lutein cysts*. Occasionally such cysts are numerous and give rise to polycystic ovaries with enlargement (Fig. 556). They represent atretic follicles with lutein formation and have been supposed to result from abnormal pituitary influence. Ovaries with such cysts have been found in a considerable proportion of cases of chorion-epithelioma and hydatid mole.

The formation of follicular cysts is supposed to be favoured by the presence of adhesions, or by superficial inflammatory change in the ovaries. It must be admitted, however, that the origin of the cysts is often obscure, as is also the relation of them to functional disturbance. A cyst may rupture into the lumen of the adherent tube and a *tubo-ovarian cyst* thus result.

Small cysts are occasionally found in the ovaries of children, and these have been ascribed to abnormalities in the formation and growth of the follicles. The term ‘small cystic degeneration’ has been applied to the condition, and manifestly larger cysts may be formed from them at a later period. It has been suggested that cystic tumours of the ovaries may develop from these small cysts.

Ovarian Hæmatomata or ‘Tarry Cysts.’ These may be formed in two ways. In the first place hæmorrhage may take place in a follicular cyst, forming a hæmatoma, and the same sometimes occurs into a corpus luteum cyst; the blood then becomes altered in colour. In the second place ‘tarry cysts’ or ‘chocolate cysts’ are met with, in which it is found that tissue like endometrium is present, and this appears to invade the ovarian tissue. The appearance, in fact, corresponds with that seen in an adenomyoma. The view now held by many is that such tarry cysts are the result of transplantation of endometrial cells, which are shed during menstruation and are sometimes carried backwards along with blood into the Fallopian tube; thence they reach the ovary and become transplanted. The new tissue gradually encroaches on the ovarian tissue and hæmorrhage occurs into it from time to time. It may be noted that at a late period the elements of the endometrium may be no longer recognisable. The lesion appears first as a hæmorrhagic area near the surface of the ovary and gradually extends till a cyst-like space filled with altered blood results The question as to the origin of such tarry cysts is the same

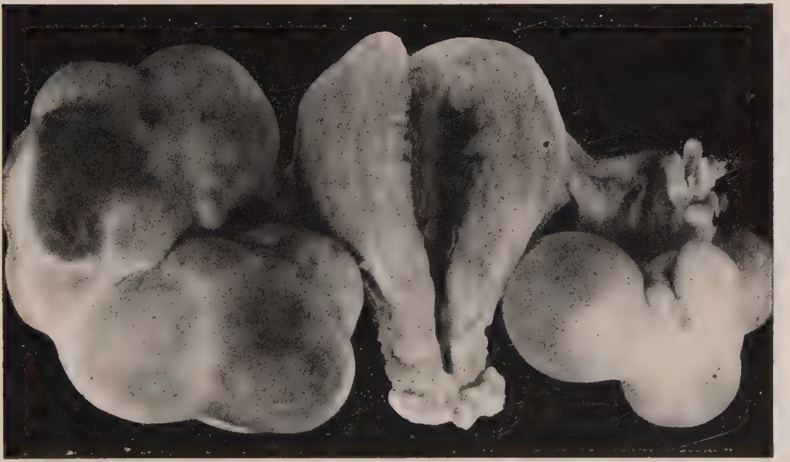

FIG. 556.—Cystic Ovaries showing large theca-lutein Cysts. The case was one of Hydatidiform Mole.

as that of endometriosis in general and has already been discussed (p. 879).

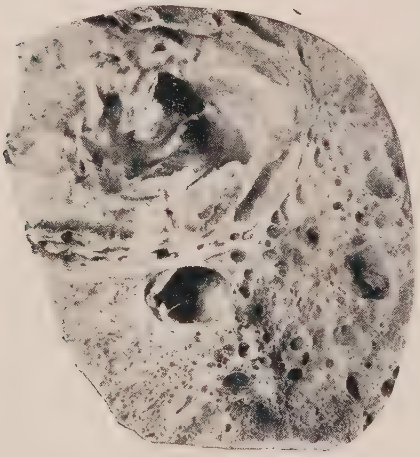

FIG. 557.—Portion of more solid part of Multilocular Cystoma of Ovary.

Note the spongy character of the tissue containing numerous cysts of varying size. × $\frac{2}{3}$.

Multilocular or Compound Ovarian Cystoma (*Cystadenoma Pseudomucinosum*). This tumour is of great importance on account of its relative frequency (it constitutes rather more than 50 per cent. of all ovarian tumours) and the serious results produced by it when left untreated. It is usually unilateral, though occasionally there is a tumour in each ovary, and not infrequently it reaches an enormous size. In pre-operation days, cystic tumours of fifty pounds weight, or even more, are recorded ; at that time they were treated by tapping, but the fluid rapidly re-accumulated owing to the enormous extent of the secreting epithelial surface. A multilocular cystoma is usually of rounded form and comparatively smooth on the surface, and though it contains numerous cysts, there is, as a rule, one of specially large size ; while at one side of the main cyst there is a more solid-looking mass of somewhat honeycomb appearance, which is composed of innumerable cysts of varying size, some being quite minute (Fig. 557). At an early stage of its growth the tumour may appear as a conglomerate of cysts, but as it grows one cyst usually comes to preponderate. The contents of the cysts are always mucoid in character, never serous, and are often of glairy or ropy nature, sometimes almost semi-solid, so that the contained material does not readily run out. On microscopic examination, the cysts are seen to be lined with a layer of tall columnar epithelium ; the nuclei of the cells are deeply placed, while the protoplasm generally is clear and mucin-containing. The lining of the spaces is thrown into folds, and in addition papillary ingrowths are of frequent occurrence (Fig. 128). The stroma is a well-formed connective tissue, which, between the smaller cysts and in the papillæ, is scanty and may form merely a thin line. The spaces contain mucoid material, along with an admixture of desquamated cells and granular débris. Although the tumour is sometimes called ‘colloid,’ the material in the contents is a form of mucin—sometimes called *pseudo-mucin*, as it is usually little precipitable by acetic acid, and its staining reactions vary somewhat as compared with those of ordinary mucin.

An ovarian cystoma, as it increases in size, rises from the pelvis, and may distend the whole abdomen. It comes to have a distinct pedicle, in which the blood vessels run, and the anatomical relations of the ovary are essentially maintained. Some important complications may be mentioned. Occasionally the pedicle is twisted and the venous return interfered with, and then the cyst wall becomes the seat of diffuse hæmorrhage and assumes a dark red colour—a condition of infarction ; blood may escape also into the peritoneal cavity. Occasionally, again, a cyst may rupture, and its mucoid contents escape into the peritoneal cavity and become diffused. The mucoid material acts as a foreign body or slight irritant, and reactive changes follow ; it is invaded by connective tissue cells and young capillaries as in a process of organisation. Transplantation of epithelial cells to the peritoneal covering also may occur and these may form acini and cysts. The result is that adhesions form between the coils of intestine and other structures, while the mucoid material still persists. The term *pseudo-myxoma peritonei* has been applied to such a condition. It may be added that malignant growth, usually in the form of an adenocarcinoma, occasionally occurs in connection with a pseudomucinous cystadenoma.

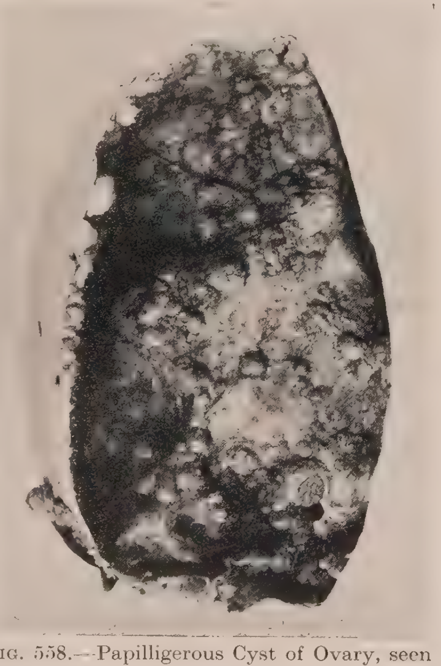

FIG. 558.—Papilligerous Cyst of Ovary, seen from within.

Note the numerous wart-like growths in the interior. × ½.

Papilligerous Cystoma. This form of growth, known as *serous cystadenoma*, is less common than the multilocular cystoma, but it is by no means rare. It may sometimes reach the size of a child's head, though usually it is considerably smaller, and in the majority of cases it occurs in both ovaries. The papilligerous cystoma consists of a single cyst, but along with the main cyst there may be some small cysts ; the contents are usually a clear, serous fluid, though sometimes a certain amount of mucin may be present. The characteristic feature is that on the inner surface of the cyst wall there are wart-like growths, or fairly large excrescences of papilliform character, the surface of which is broken up into numerous projections, somewhat resembling a cauliflower (Fig. 558). These papillomata are covered by columnar or cubical epithelium which is often ciliated, but the cells have not the mucin-forming character seen in the multilocular cystoma, and their nuclei are less deeply placed (Fig. 559). A cystoma of this kind grows somewhat slowly, and, as has been stated, never reaches the great size of the multilocular cystoma. Not infrequently, however, the cyst wall ruptures, and the contents along with portions of papillomata escape into the peritoneal cavity. The pieces of tumour are distributed by the intestinal movements, and then become attached to and grow on the peritoneal surface, which may thus come to be beset with numerous excrescences (Fig. 560). Their growth is usually attended with marked ascites. After operative removal of the primary growths, the peritoneal growths may undergo atrophy, but usually they continue to grow. Sometimes the surface of both ovaries is covered with papillomatous growths, and there may also be a single cyst or several small cysts in the ovaries. True carcinoma not infrequently develops in connection with a papilligerous cystoma; this is much commoner than in the case of the multilocular cystoma.

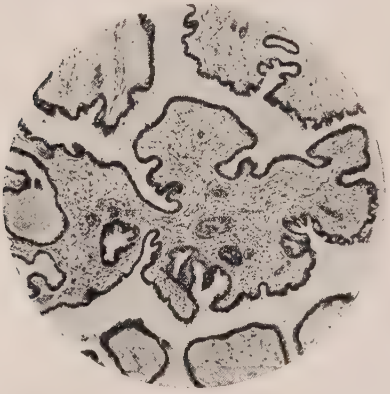

Fig. 559.—Portion of Papilligerous Cyst of Ovary, showing the Papillæ covered by Columnar Epithelium. × 40.

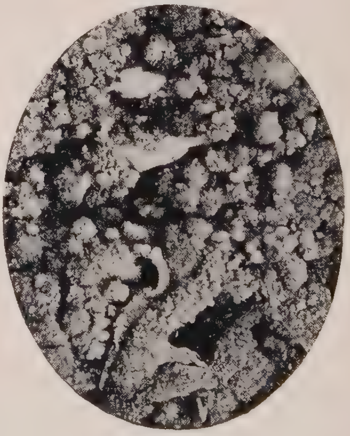

Fig. 560. — Papillomatous Mass from Omentum—a transplantation from a Papilligerous Ovarian Cyst. (From same case as Fig. 559.) × $\frac{2}{3}$.

Although the cystomata of the ovary may be regarded as the result of abnormalities in development, there is still doubt regarding their exact origin. The multilocular cystoma was generally supposed to arise from the epithelium of the follicles, or from the tubules or cords of cells from which these are formed, but on such a view it was difficult to explain satisfactorily the peculiar characters of the cells of the tumour. The view which has now most support is that the tumour is really of teratoid nature, in which there is a special growth of one of its component tissues, namely, a tall mucin-forming epithelium. The origin of the papilligerous cystoma is generally ascribed to the germinal epithelium of the surface of the ovary.

Teratomata. The commonest is the cystic teratoma or 'dermoid' cyst. The latter term is applied owing to the cyst being lined by squamous epithelium, and to the prominence of skin structures; but the tumour is really a teratoma. The growth is usually single, but occasionally there is one in each ovary; and cases have been recorded in which more than one have been present in an ovary. It often forms a rounded swelling which may reach the size of a child's head, but is usually smaller. The contents are fatty material, which is fluid at the temperature of the body, but becomes semi-solid on cooling; and mixed with it are hairs, desquamated epithelium, etc. As has been said, the lining is a stratified epithelium, and the skin structures—hairs, sebaceous and sweat glands—are abundantly represented. At one side there is often a somewhat hard protuberance, and on the inner surface several teeth, irregularly arranged, are often present (Fig. 561). On section this projection contains bone and other structures—cartilage, non-striped muscle, various glandular structures representing alimentary and respiratory systems; occasionally chorionic epithelium has been found, and even nervous tissue may be present. No trace of the reproductive glands, however, has been observed in these growths. Cystic teratomas vary much as regards their complexity of structure, and not infrequently epidermal structures preponderate. Less common than this cystic form is the solid form of teratoma, which usually forms an irregular rounded mass, in which an even greater variety of tissues may be found; small cysts may be present in it. In the testicle, on the other hand, the solid type is the one more frequently met with. The significance of these growths is discussed on p. 261. Malignant disease often develops in connection with a

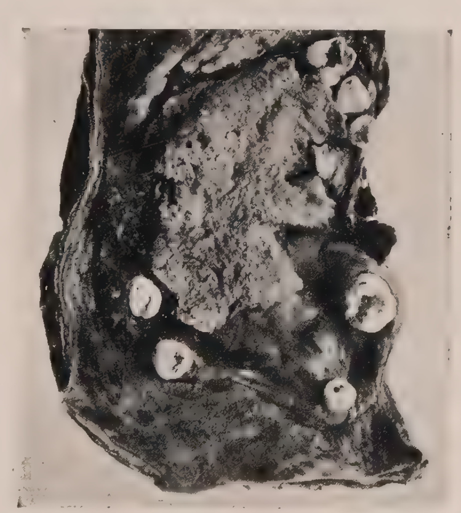

FIG. 561.—Portion of Wall of Teratoma of Ovary (Dermoid Cyst), showing irregular Growth of Teeth from inner surface of Cyst.

teratoma of the solid type; the growth is usually a carcinoma, rarely a chorion-epithelioma or a sarcoma. It is a rare occurrence in the case of cystic teratoma.

Parovarian Cysts. These cysts, which are of fairly frequent occurrence, are derived from the epoophoron or anterior part of the parovarium or Wolffian body, which lies in the broad ligament between the ovary and the tube, the cysts having a corresponding position. They are usually single, spherical in form, and consist of one chamber. Their contents are a clear watery fluid with low specific gravity, in which there is little or no albumin and no mucin. They are usually lined by a ciliated columnar epithelium, though in places the layer may be of the cubical type. As the cyst increases in size, it separates the layers of the broad ligament, and is thus covered by a layer of peritoneum, which, however, is separable from the cyst. The tube is stretched over the surface, whilst the ovary lies at the other side and may undergo atrophy. Usually there is no distinct pedicle, but if the cyst is very large it may rise from the broad ligament and have a broad pedicle.

Malignant Tumours. The malignant growths of the ovary present a considerable variety, and fairly often are associated with cyst formation. Carcinoma is much more frequently met with than sarcoma.

It is to be noted that *carcinoma* in the ovaries may occur at a comparatively early period of adult life. The growth is not seldom in both ovaries, but that in one is often considerably larger than that in the other. It presents the usual features, but varies in type, being sometimes hard and nodular, sometimes comparatively soft and leading to great enlargement. It may burst through the capsule and produce secondary growths in the peritoneum, as well as metastases in the regional glands and in other organs. Histologically, considerable variations in structure are met with. The cells may be arranged in solid masses as in scirrhus of the breast, or they may have an irregular acinous formation; or, again, in the softer varieties, a more diffuse manner of growth may be present, with great aberration in the characters of the cells. Carcinoma sometimes becomes superadded to a cystic tumour, either of the multilocular or papilligerous variety, but more frequently of the latter.

Krukenberg described a bilateral tumour of the ovaries under the term '*fibrosarcoma mucocellulare carcinomatodes*'; it is now called after him. There is a very cellular sarcoma-like stroma in which cancer cells are scattered or occur in masses. Many of the cells contain mucin which has pushed the nucleus to one side, giving a signet ring appearance. Secondary growths of cancer in the ovaries have, however, been found to present similar characters, and it is now generally considered that the Krukenberg tumour is not of ovarian origin.

Other forms of ovarian tumours have recently come to be recognised and two of these, viz. the granulosa-cell tumour and the arrhenoblastoma, are specially interesting in view of their hormonal effects.

Granulosa-cell Tumour. This growth, which is also known as *folliculoma* or *carcinoma folliculoides*, is generally believed to arise from granulosa cell rests which have not been used up in the formation of Graafian follicles. It is composed of moderately firm and fairly cellular tissue, sometimes of a yellowish tint, and cysts, usually small, may be present. The microscopic appearances vary considerably. The cells are often rounded or polyhedral with somewhat clear cytoplasm, often containing lipoids, and of inactive appearance. They are arranged in solid, well-defined masses like a carcinoma ; sometimes, however, they are more cubical or columnar and have an acinous or follicle-like arrangement (Fig. 562). In some specimens the growth is of a diffuse character resembling sarcoma, though in parts evidence of the characteristic arrangement of cells is usually to be found. The histological characters may vary much in different parts of the same growth. Such tumours are usually unilateral and of rather low malignancy. They have been met with most frequently after the menopause but they occur at other ages. At all periods they have a distinct hormonal effect which corresponds to the formation of œstrone in excess—*hyperfolliculinisation*. After the menopause the effects are hyperplasia of the endometrium and enlargement of the uterus, with uterine bleeding which is usually periodic—pseudomenstruation ; during the child-bearing period the effects are of a

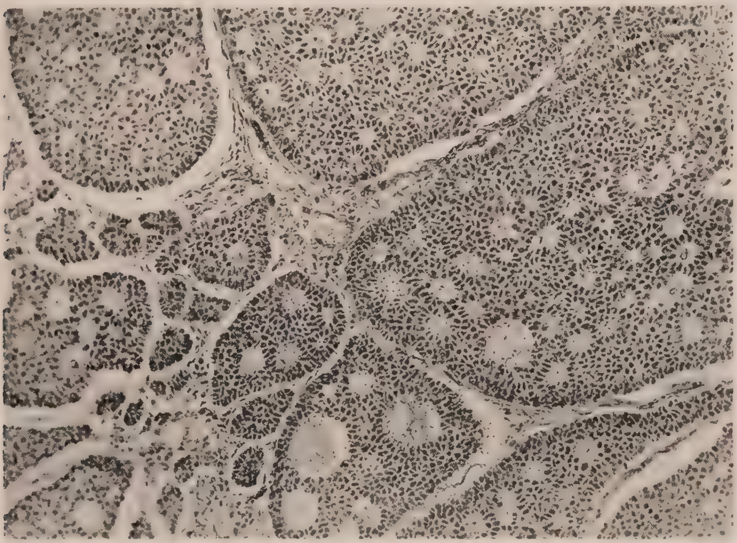

Fig. 562.—Granulosa-cell tumour of Ovary, showing characteristic masses of cells with tendency to follicle formation. (Prof. M. J. Stewart.) × 150.

similar kind. In the few cases observed in young girls the effects are of striking nature, there being precocious puberty, establishment of menstruation and development of the secondary female sex characters. That these growths exert an endocrine influence is shown by the fact that the symptoms and signs have been repeatedly found to disappear when the growths are removed.

An interesting fact is that in a small proportion of cases the granulosa cells may undergo a transformation into lutein cells, and then the effect on the endometrium is like that of progestin.

Brenner Tumour. This ovarian growth, which is much less common than the granulosa tumour, was for a time confused with it. It was called by Brenner *oophoroma folliculare*. It varies greatly in size and it has a firm consistence, sometimes resembling a fibroma. Microscopic examination shows an abundant and dense fibrous stroma in which are scattered islands or nests of epithelial cells. These islands may be solid collections, but very often show a circular central space (Fig. 563). The cells are rounded or polyhedral and are comparatively uniform and inactive in appearance. An interesting point is that sometimes the cells lining the space assume a columnar form, resembling those in a pseudo-mucinous cystoma. The tumour is slowly growing and may be regarded as of simple character. It is generally believed to take origin from collections of indifferent cells, often known as Walthard's nests or inclusions, which are found in the superficial parts of the ovaries in infants. A noteworthy fact is that unlike the granulosa cell tumour, the Brenner tumour shows no evidence of having any endocrine effect.

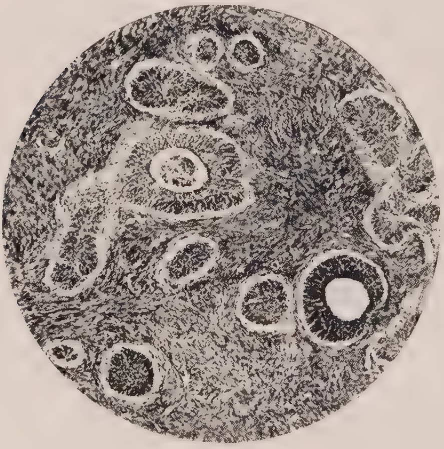

FIG. 563.—Brenner Tumour of Ovary.
Showing characteristic features as described in text. (D. F. C.) × 45.

Arrhenoblastoma. This growth, which also is of rare occurrence, is supposed to arise from 'male-directed' cells in the region of the rete ovarii, persisting from an early period of gonadogenesis. It may be of an adenomatous type containing structures somewhat resembling tubules of the testis, but the structure may be more atypical and not unlike that of a sarcoma. The hormonal effect, which has been more pronounced in atypical growths, is like that of the adenoma of the adrenal cortex, namely, the production of virilism or an intensification of maleness. In a previously healthy woman there may occur atrophy of the uterus and mammæ, amenorrhœa, and the appearance of the secondary male sex characters. It has been met with chiefly in young women. Removal of the growth has been followed by the disappearance or modification of these abnormalities. Its malignancy is of low order.

Another rare form of ovarian tumour is the *dysgeriminoma* (R. Meyer). Histologically it corresponds closely to the seminoma and it has been called *seminoma ovarii* by French writers. It is supposed to arise from undifferentiated sex cells and does not exert hormonal influence; that is, does not accentuate masculine or feminine characters. It may develop at a relatively early age, and has accordingly been called *carcinoma puellarum.* In a fairly large proportion of cases it has been associated with infantilism or with pseudohermaphroditism. Its removal, however, has no effect on these abnormalities. Its malignancy is usually said to be of low order, but in some cases extensive metastases occur.

Secondary carcinoma of the ovaries is comparatively frequent and of considerable interest. It is met with in carcinoma of the stomach and intestine, and though nodules may be present over the peritoneum, this is sometimes not the case. The secondary growths sometimes reach a large size. It would seem as if the ovarian tissue were a specially favourable nidus for growth, and that a few cancer cells gaining access to the peritoneum had a marked tendency to become located in the ovaries. It is possible also that in a similar way a cancer may pass from one ovary to another without causing nodules in the peritoneum. It may be noted too that secondary growths are not uncommon in cases of cancer of the breast ; the manner of spread is doubtful—possibly in this case also it occurs by the peritoneal cavity. The Krukenberg tumour is usually a variety of secondary carcinoma (p. 890).

Sarcoma, though less common than carcinoma, is by no means rare. Like the latter, it sometimes affects both ovaries and may occur in association with cysts ; the growth may reach a large size. Usually the tumour is of the spindle-cell type and has a somewhat fasciculated appearance on section ; forms intermediate between fibroma and sarcoma are met with. Round-cell and mixed-cell varieties also occur. Angiosarcoma, various types of endothelioma, and sarcoma combined with carcinoma, have been described.

Congenital Abnormalities

These are of considerable variety and are brought about in different ways. They may be due to failure in the normal fusion of parts, to incomplete development or absence of certain structures, to pathological closure or atresia of openings etc. ; and there is also the important group of abnormalities due to displacements of cells or portions of tissue, from which certain tumours arise ; this is seen especially in the case of the ovaries.

UTERUS. Certain abnormalities arise from variations in the fusion of the lower parts of the ducts of Müller. It may be recalled that the upper portions of the ducts constitute the two Fallopian tubes, whilst the lower portions coalesce to form the uterus and vagina. From imperfect fusion there arises duplicity of structures which are normally single, and various degrees of such a condition are met with. Thus there may be a double uterus and vagina, a double uterus and single vagina (uterus bicornis duplex), or the uterus may be doubled only in its upper part (uterus bicornis unicollis) ; then again there are variations according to the degree in which the walls of the doubled cavities are fused. In the slightest degree of this type of abnormality the uterus has two short cornua and the outline of the fundus is concave upwards instead of convex, the condition being known as *uterus arcuatus.* Occasionally the ducts of Müller have split in their upper part, so that there are two Fallopian tubes on each side ; or the splitting may be only partial, but this is a rare abnormality.

Deficiency of growth or *aplasia* is likewise of varying degree. Absence of the uterus and tubes is the extreme example of such a condition, but is very rare ; absence of uterus or of its lower part is occasionally observed while the tubes are present. Then again the uterus may be well formed, whilst there is occlusion or atresia of the os, less frequently of the isthmus; such lesions may lead to accumulation of the menstrual blood. Occasionally one duct of Müller has failed to develop, and then there is an absence of one tube, whilst the uterus is asymmetrical —*uterus unicornis.* In other cases asymmetry is due to a rudimentary cornu on one side, which is sometimes cut off from the uterine cavity. There are also other variations in which a tube or part of a tube is absent. Portions of the Wolffian ducts may fail to undergo the usual obliteration and may persist in the wall of the vagina; they may there give rise to cysts or tumour growths. The normal division of the cloaca with formation of septum may be incomplete, and thus there remains a communication between the vestibulum and the lower end of the rectum—vestibulo-rectal fistula. This condition may be associated with imperforate anus (p. 581).

General *hypoplasia* of the uterus is observed in ovarian defect and may be attended by other abnormalities, e.g. pseudo-hermaphroditism, which condition is sometimes associated with hyperplasia of the adrenal cortex (p. 923). Hypoplasia, or rather the persistence after puberty of the infantile type of uterus, is seen in conditions of infantilism, for example that resulting from deficiency of the thyroid or of the anterior lobe of hypophysis.

OVARIES. As already indicated, the most important abnormalities are those affecting the disposition of the germinal epithelium and the formation of the Graafian follicles; the various cystic tumours of the ovaries probably arise in this way. Small cysts of congenital origin are occasionally met with, and may be associated with a certain amount of fibrosis. The ovaries are sometimes abnormally small, and there is then usually a condition of hypoplasia of other parts of the genital system; occasionally pseudo-hermaphroditism is present. True doubling of the ovaries has been recorded, but it is extremely rare; aberrant portions of ovarian tissue are, however, occasionally observed. Lastly, one or both ovaries may be in an abnormal situation, for example, one may be present in a patent canal of Nuck.

ABNORMALITIES IN CONNECTION WITH PREGNANCY

The pathology of pregnancy is a wide subject, and it would be beyond the scope of this work to consider it in detail. We shall, however, give an account of some of the chief abnormalities which are of special interest and importance.

Hydatidiform Mole. This is a somewhat remarkable condition, resulting from an affection of the chorionic villi attended by great enlargement. These are changed into rounded or oval structures of the size of currants, or even small grapes, and, as their covering is smooth and tense, they have much the appearance of the latter (Fig. 564). On microscopic examination, the substance of the villi is seen to be myxomatous tissue in a condition of extreme œdema, and often little mucus is present. On the surface the chorionic epithelium often shows signs of proliferation, there being several layers of Langhans cells, and the syncytium is correspondingly prominent; the surface in places may, however, be denuded of epithelium (Fig. 565). In some cases the ‘ mole ’ is constituted mainly by altered villi, and there is no trace of fœtus, or true placenta; the villi in such cases penetrate and destroy the decidual layer in an irregular manner. In other cases where the change has occurred at a later period, a small imperfectly developed embryo may be found lying in its sac, and placenta may be present in which the villi are embedded ; in fact, varying degrees of the mole condition are met with. Hydatidiform moles may sometimes reach a weight of two or three pounds, and their presence is often attended by an abnormally rapid increase in the size of the uterus. They lead to abortion, which is often preceded by hæmorrhage, sometimes of a serious nature ; the blood may be retained and form firm coagula which result in the condition of so-called 'fleshy mole' in addition. There are also cases in which the villi of the mole show much more extensive penetration, extending into and destroying the uterine wall and thus approximating to a malignant growth in character—the so-called 'invasive mole.' And lastly, not infrequently malignant properties are assumed by the chorionic epithelium on the altered villi, the growth then constituting a chorion-epithelioma. The cause of hydatidiform mole is unknown, but the fact that cases of twin pregnancy have been recorded in which a mole has been present along with a

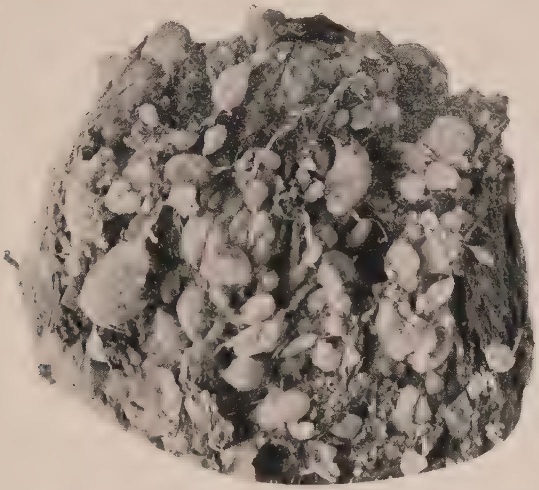

FIG. 564.—Portion of Hydatidiform Mole, showing the enlarged grape-like Chorionic Villi.

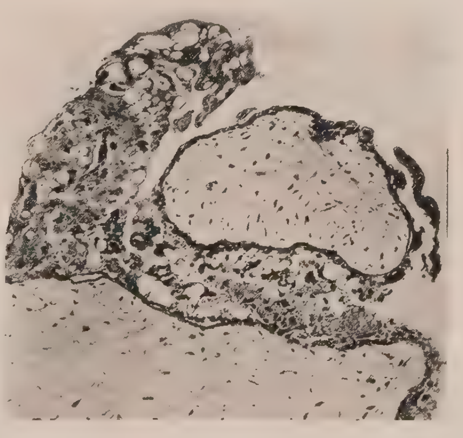

FIG. 565.—Hydatidiform Mole, showing the œdematous Tissue of the Villi, covered by Langhans Cells and Syncytium. × 75.

normal fœtus, points to the original change being in the ovum rather than in the uterus. It is noteworthy, however, that the hydatiform mole, like chorion-epithelioma, is often associated with theca-lutein cysts in the ovary (Fig. 556).

Chorion-epithelioma. This tumour is essentially composed of the epithelial cells covering the villi of the chorion, which have acquired invasive and malignant properties, both the cells of Langhans and syncytia taking part in the proliferation. It is of special interest as representing an invasion of the maternal tissues by fœtal cells. It may develop during ordinary pregnancy and give rise to abortion or premature delivery. Or it may develop after delivery, no doubt from portions of retained placenta. Its occurrence has been occasionally observed several years after a pregnancy or miscarriage. But in nearly half the cases it is a sequel to a mole pregnancy, and, as has been stated, the infiltrating mole represents a transitional form. As we have said, the tumour is essentially composed of the two elements of the chorionic epithelium. The Langhans cells, which are rounded or polyhedral, with badly defined margin, often form large masses, on the surface of which are the large syncytial cells. The latter present a great variety of shapes, and often have long trailing processes; their protoplasm is finely granular and more eosinophile than that of the Langhans cells (Fig. 163).

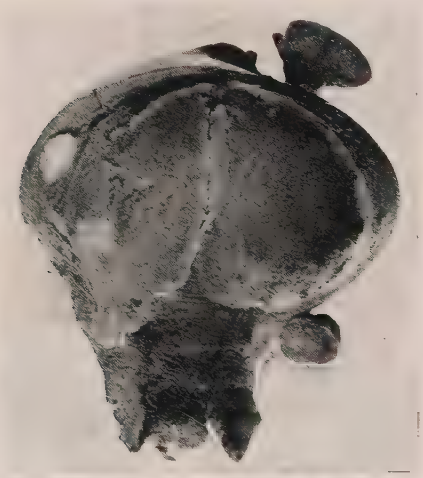

FIG. 566.—Chorion-epithelioma of Uterus.

Note the large hæmorrhagic mass in the interior of the uterus; the pale nodule in the wall on the left-hand side is a small myoma. × ½.

These appearances are best seen in the younger and actively growing parts of the tumour, but in other parts the arrangement is more irregular, the two kinds of cells being mixed together. There is little stroma, and the growth has no blood vessels of its own; areas of necrosis and extravasated blood are usually present (p. 247). The tumour in the interior of the uterus appears as a soft cellular mass, often of crumbling texture and of a dark red colour, owing to hæmorrhages (Fig. 566): these are the result of erosion of the blood vessels by the syncytial cells. It causes absorption of the uterine wall, and may penetrate to the peritoneal coat. Secondary growths, which occur chiefly by the blood vessels though also by the lymphatics, are frequent, their commonest sites being in the lungs, vaginal wall, lymphatic glands, and liver (Fig. 393). The secondary growths have the same general characters as the primary, and are usually very hæmorrhagic and necrotic. Occasionally a secondary nodule in the lungs may undergo complete necrosis, and then it may become enclosed in a fibrous tissue, so that a process of local healing takes place (Teacher).

Chorion-epithelioma has been observed to originate in a Fallopian tube or an ovary, and in such cases it apparently develops in connection with an ectopic pregnancy. It may be added that in cases of chorion-epithelioma or hydatidiform mole the urine as a rule gives a distinct Ascheim-Zondek reaction for pregnancy, the reacting substance being often present in greater concentration than in a normal pregnancy. This substance was at one time believed to be prolan, a product of the anterior pituitary, but it is now recognised to be formed by the trophoblast. It is often known as A.P.L. (anterior-pituitary-like) substance. The reaction becomes negative if the growth is removed, and the test can be applied in following the further course of the case. In a considerable proportion of cases of chorion-epithelioma or hydatidiform mole the ovaries have been found to be enlarged and cystic, the cysts being of the theca-lutein type (p. 884).

It may be added that structures of the character of chorionic epithelium may be present in teratomata, e.g. of the testicle, mediastinum, etc., and that chorion-epitheliomata may arise from them. This can be understood in view of the fact that nearly every fœtal tissue may be represented in such growths. In these growths also a positive Ascheim-Zondek reaction is obtained.

Extra-uterine Pregnancy. This condition arises when the fertilised ovum becomes implanted and develops before it reaches the uterus. It may occur (*a*) in the Fallopian tube, (*b*) between the outer end of the tube and the ovary, when these are adherent, (*c*) in the ovary itself, or (*d*) in the peritoneal cavity ; and the terms *tubal*, *tubo-ovarian*, *ovarian*, and *abdominal*, are applied respectively. All these forms, with the exception of the tubal, are rare.

Abdominal pregnancy is usually secondary to rupture of a tubal pregnancy, the ovum being then implanted on the peritoneal surface ; but a primary form also is recognised. In the tube the commonest site is in its free portion, but the implantation is sometimes met with in the tube as it passes through the uterus, the pregnancy being then known as *interstitial*. It is generally accepted that tubal pregnancy is in most instances the result of some abnormal condition of the tube—usually a chronic inflammatory change, which probably acts in two ways. On the one hand, the ciliated epithelium, to which the passage onwards of the ovum is believed to be due, is lost ; and on the other hand, pockets or depressions are formed in which the ovum tends to lodge. Within the tube the ovum passes through the mucosa and develops underneath it or in the muscular layers. The fœtal structures are formed in the usual way and there is great development of blood vessels around (Fig. 567) ; but decidua is not formed, or its formation is only imperfect. The surrounding structures are absorbed by the chorionic villi as well as stretched by the growing ovum. Rupture of the blood vessels is common at a comparatively early period, and the hæmorrhage tends to separate the ovum from the surrounding tissues. Rupture into the peritoneum, which is common, is usually attended by severe hæmorrhage, and this may lead to a fatal result, even at a quite early stage of the pregnancy. Occasionally the placenta becomes separated from the ruptured tube and then attached to the peritoneum. The fœtus may then reach various stages of development, abdominal pregnancy of the secondary type resulting. The fœtus may die and become encapsulated, and at a later period may be the seat of calcification, the result being known as a *lithopædion*. In a considerable number of cases a live child has been removed by operation from the peritoneal cavity. It is to be noted that in extra-uterine pregnancy a decidua forms within the uterine cavity and may become separated and passed. Cases are on record where chorion-epithelioma has developed in a tube as a secondary result of tubal pregnancy.

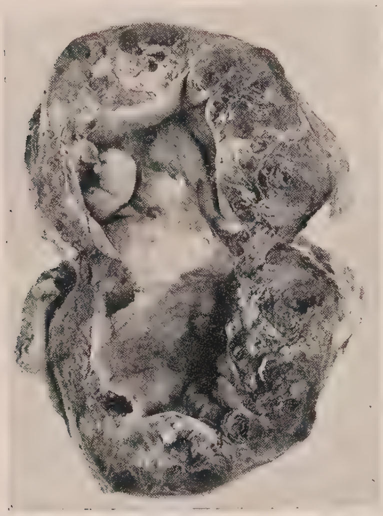

FIG. 567.—Section through Tubal Pregnancy, showing the very Vascular Wall; the Embryo is seen in the upper portion. × $\frac{2}{3}$.

Syphilis of the Placenta. Important structural changes are produced in the placenta by syphilis, but it is often impossible in any given case to say whether a lesion present is syphilitic or not. In many undoubted cases of syphilis the placenta is heavier in relation to the child than normally, and its consistence is somewhat denser and its colour paler. The chief change is an increase of the connective tissue of the villi, sometimes attended by growing together of villi. This change leads to a diminution in the blood supply and thus interferes with the nourishment of the child. While spirochætes have been found in some cases, they occur only in small numbers; and in many cases, even when the internal organs of the fœtus are swarming with the organisms, it is not possible to find any in the placenta. Accordingly, while the organisms can readily pass through the placenta from the maternal to the fœtal blood, the placental tissue does not form a suitable soil for their growth. And in any given case, the question as to the presence of syphilis is much more likely to be answered by an examination of the fœtus than of the placenta.

It is especially to be noted that the presence of necrotic areas or *infarcts of the placenta* must not be taken as evidence of syphilis. These infarcts may be of considerable size and in considerable numbers; they are usually irregular in form, of yellowish white or pale red colour, and of dull necrotic appearance. Such infarcts occur in a variety of conditions, and those of smaller size are not uncommon. While syphilis may favour their occurrence, nothing definite can be inferred from their actual presence.

Tuberculosis of the Placenta. This affection, which is comparatively rare, may occur in either of two ways. It may be due to spread from tuberculous disease of the endometrium, or it may occur in acute miliary tuberculosis of the mother. In the latter case, the bacilli settle on the epithelial covering of the villi and then penetrate their substance and give rise to tubercles. Infection of the fœtus may follow, and thus a congenital form of tuberculosis, usually of miliary type with marked affection of the liver, is produced. But such an occurrence is very uncommon and plays a trifling part in the spread of the disease; and the vast majority of cases of tuberculosis in very young infants are the result of infection after birth.

MAMMA

Inflammatory Changes

Of acute inflammatory conditions of the female mamma two main forms are usually recognised, a non-suppurative and a suppurative, and these have widely different results.

(*a*) **Acute Non-suppurative Mastitis.** The commonest type occurs in connection with lactation, and is thus a form of puerperal mastitis; it is mainly a condition of congestive swelling and œdema, though attended by some pyrexia. It may result from blocking of ducts or from early stoppage of suckling. A somewhat similar type of inflammatory lesion may be met with at puberty.

(*b*) **Acute Suppurative Mastitis.** The most important form of this lesion is a suppurative condition which, like the above, is specially related to lactation, and is the result of bacterial infection by the ducts or through some abrasion or fissure of the nipple. It is usually caused by staphylococci, sometimes by streptococci. As a rule there are several foci of suppuration which may become confluent and form a somewhat loculated abscess, and great destruction of the breast may result; sometimes, especially in cases of streptococcal infection, the condition spreads diffusely and is of a phlegmonous type. When the abscesses are of small size they may become encapsulated and lead to much overgrowth of connective tissue around an irregular induration, the condition of the breast coming to resemble that seen in primary chronic mastitis. The suppuration usually occurs in the breast tissue itself—*intra-mammary* abscess, and the organisms spread by the ducts as well as by the lymphatics. Sometimes it is in front of the breast—*pre-mammary*, and is the result of lymphatic infection from the nipple; or occasionally behind it—*retro-mammary*, usually due to extension from abscess in the breast. Suppuration in the breast may occasionally occur as the result of blood infection, but this is rare.

Chronic Mastitis. Under this heading are usually included a variety of conditions in which hyperplasia of epithelium, cyst formation and interstitial overgrowth are present in varying combinations. The great majority of such conditions, however, are of the nature of nutritional disturbances and are not of inflammatory nature; these will be considered under a separate heading. Chronic mastitis, in the strict sense, is a localised lesion which may follow acute mastitis or occasionally prolonged lactation. It may also result from a blow and may then be associated with fat necrosis. Local fibrosis may occur also from chronic suppuration, syphilis or tuberculosis, and is occasionally met with in breasts removed for other conditions supposed to be present. All these lesions present the usual characters and need no description.

Traumatic Fat Necrosis. This lesion is usually in the form of a localised firm or even hard mass in the mammary tissue. It may underlie and be adherent to the skin and has not infrequently been mistaken for carcinoma. There is a history of traumatism in most cases but not infrequently this cannot be obtained; the lesion has occasionally been observed after operations. The appearances vary at different stages but there is often a central cavity or pseudocyst containing oily fluid which may be brown in colour. This is surrounded by a broad zone of dull yellowish white tissue almost of chalk-like appearance, with scattered areas of similar appearance in the outer part. At the periphery there is a zone of enclosing connective tissue. Microscopic examination shows the presence of cells of two types, namely rounded foamy cells containing small fatty globules and multinucleated giant-cells which may form large collections. Many of the giant-cells contain crystals of fatty acid and at places a number of them may be arranged around masses of crystals. There appears to be usually comparatively little doubly-refracting fat. The lesion represents the result of necrosis followed by a slow lipolysis along with phagocytosis and other reactive changes towards the products of disintegration.

Tuberculosis. It is often stated that tuberculous infection of the breast is of rare occurrence, but in our experience it is not very uncommon. It may be the result of hæmatogenous infection, a few bacilli being carried by the blood stream from some other part, or it may be due to lymphatic spread from some lesion in the vicinity, for example, from caseous axillary lymphatic glands or tuberculosis of the pleura or ribs. The bacilli settle in the interstitial tissue, invade the lobules, and cause the formation of tubercles which may spread to the sub-epithelial connective tissue of the ducts and acini. Ulceration may then occur into them and the bacilli may be spread by means of the ducts. Sometimes the affection may be comparatively localised and lead to a large swelling which may simulate a tumour growth; sometimes, again, the lesion may be more of the nature of a diffuse infiltration with nodular thickenings, and thus it may resemble a chronic interstitial mastitis. In untreated cases, the caseous change may spread to the surface of the breast and ulceration with formation of a sinus may result.

Syphilis. The primary sore sometimes occurs on the nipple when a wet nurse suckles a child affected by congenital syphilis. In the secondary stage the usual papules, mucous patches, etc., may be met with. Gumma of the breast is comparatively rare. We have seen a considerable amount of necrosis of the breast tissue occur as the result of this lesion, and the structural outlines of the dead tissue may be maintained for a considerable period of time. As in other parts, a gumma may undergo fibrous contraction. There is little doubt that primary local fibrosis of the breast may be produced by syphilis, but unless gummatous change also be present, there is no means by which its nature can be definitely recognised, unless, of course, by the finding of spirochætes.

Actinomycosis. A few cases of this infection have been recorded, but the condition is very rare. It has been known to extend to the breast through the chest wall from the pleura.

Hyperplastic Cystic Disease. This seems a suitable term for conditions in which there is a remarkable variety of epithelial changes, both metaplastic and hyperplastic, often associated with cyst formation. In some cases cyst formation, in others epithelial hyperplasia is the prominent feature ; and the proportion of these changes may vary in different parts of the same breast. The term which we have used corresponds in a general way with *mastitis chronica cystica*, ‘ Schimmelbusch's disease ’ and the *cystiphorous desquamative epithelial hyperplasia* of Cheatle. The condition is also spoken of as *mastopathy*, a term which is convenient but actually of too comprehensive significance. It may be conveniently described as occurring in two forms, a generalised and a localised.

The *generalised* type occurs most frequently in childless women and is often associated with menstrual disturbance ; it tends to be progressive. Starting locally, it comes to affect the breast generally, and both breasts may be involved, either simultaneously or one after the other. The connective tissue in the affected parts is increased in consistence and has a coarse or somewhat nodular character to the touch ; and, on section, small cysts of varying size are present in the indurated lobules. The cysts are usually smaller than a pea, often quite minute and arranged in clusters, and the breast may be studded with them. Occasionally one or more may reach a large size. Their contents are a somewhat thin mucoid fluid which varies in colour.

On microscopic examination the structural features are found to be of great variety, but they may be arranged under the following three headings, viz. (*a*) cyst formation, (*b*) epithelial hyperplasia, and (*c*) fibrosis. Cyst formation begins by dilatation of ducts, though acini also become implicated. It appears to depend upon an abnormal secretion by the epithelial lining, though subsequent obliteration of ducts may play a part; it is accompanied by proliferation and desquammation of cells and also by metaplasia, a not uncommon example of the latter being an increase in the size of the cells attended by feathery appearance and increased eosinophilia of the protoplasm. Some writers regard this eosinophile epithelium as a homologue of sweat-gland epithelium, but we have been unable to find sufficient evidence for this. Certainly we have been able to trace transitions between it and the ordinary type of epithelium, both within cystic spaces and on the surface of papillomata, and it has been shown that spaces lined by the eosinophile type are in direct communication with ducts. The hyperplastic change affects the acini, there being at places increased formation by budding or by ingrowth of papilliform processes. The latter, however, is most marked within the ducts and not infrequently there are broad branching processes covered with epithelium as in the ordinary duct papilloma. In other cases, the stroma of the papilliform growths is in finer bands and the epithelium is more abundant. In other cases again, there is almost no stroma, the epithelial cells forming large masses which may show at places a tendency to acinous arrangement. As a final stage, though this is much commoner in the localised form of the disease, ducts may be lined by several layers of irregularly arranged epithelial cells or be filled with masses of these; their nuclei are often hyperchromatic or show aberration in type, and the whole appearance is that of malignant neoplasia. The term *intraduct carcinoma* may then be suitably applied (Fig. 575).

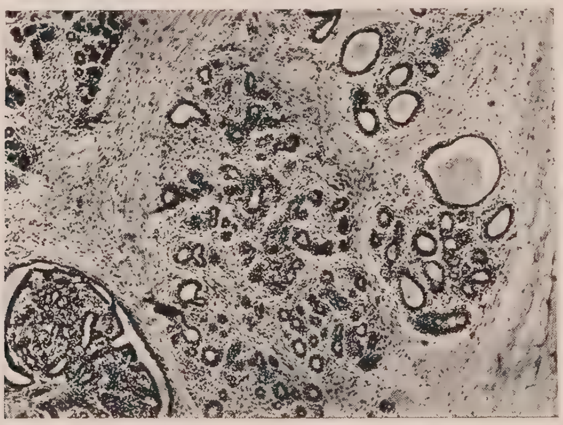

FIG. 568.—Hyperplastic Cystic Disease of Mamma.

Note fibrosis around acini and formation of small cysts at places; a small papillomatous growth within a duct is seen on left-hand side. × 45.

A corresponding change may occur within acini, resulting in intra-acinous carcinoma (Fig. 576). From either lesion a break through of the malignant cells may follow and lead to ordinary infiltration of carcinoma.

The accompanying fibrosis (Fig. 568) varies greatly in its amount and distribution. It often occurs around the acini and leads to their atrophy. At a late stage there may be present a comparatively acellular connective tissue in which ducts and acini are scanty. Hyperplasia of stroma may also occur in association with that of epithelium and there are not infrequently small tumour-like nodules of the intracanalicular type (p. 904).

Cystic change may occur also about the time of the menopause or thereafter, and may affect both breasts. It is apparently the result of abnormality in the process of involution of the mammary tissue.

The *localised* hyperplastic disease is much commoner. It usually starts in the child-bearing period, in other words, before the cancer age. A certain amount of pain may result, but very often the condition is symptomless. It may give rise to irregular induration and call for surgical removal. On the other hand, we believe that it very often escapes notice, and clear evidence of its frequent incidence is got from examination of breasts removed for carcinoma. My experience is that in the great majority of cases of carcinoma a lesion of this kind can be found as a pre-existing condition ; with regard to this I am in agreement with Cheatle. The changes are of similar nature to those described in the generalised forms but cyst formation is often slight or absent, and the main changes are forms of epithelial hyperplasia, terminating not infrequently in intraduct carcinoma.

The relation of hyperplastic cystic disease to carcinoma is still a matter of controversy. That the former is not infrequently a precancerous condition I consider to be undoubted, but in what proportion of cases, it is not possible to say. My own experience is that it is not common to find carcinoma developing in a breast which would be clinically recognised as definitely cystic. On the other hand, in breasts removed for cancer it is practically the rule to find localised hyperplastic disease. The lesion is often of such a nature that would remain undetected clinically. Some further facts are given below.

Etiology. There is no evidence that cystic hyperplasia is the result of inflammatory change caused by micro-organisms or in some other way ; the use of the term ‘ mastitis ’ is thus not justifiable. The changes described, especially those in the more generalised type of the disease, rather represent the effect of widespread nutritional disturbance brought about by endocrine agency. This view has received strong support from the experimental work in recent times. It has been shown by Lacassagne and others that injection of œstrone in male mice brings about growth and other changes in the rudimentary mammary tissue and that carcinoma may follow. These results do not show that cystic hyperplasia is the effect of excess of œstrone, but they are decidedly in favour of the view that it represents the result of disturbance of endocrine balance. It is known, for instance, that lutein is concerned in the various cyclical changes naturally occurring in the mamma and its action also may be disturbed. At present, however, the real nature and causation of the supposed hormonal disturbance are unknown.

Hypertrophy. The so-called hypertrophy of the mammæ is really a pseudo-hypertrophy. The condition usually develops shortly after puberty, though sometimes at a later period in connection with pregnancy. It is characterised by a progressive enlargement and ultimately the mammæ may reach an enormous size, so that they may weigh several pounds. The enlargement is due to a great increase of the connective tissue, which is soft and œdematous, and also of the adipose tissue, the proportion of the two tissues varying in different cases; sometimes the amount of fat is not great. There is usually no actual increase of the glandular tissue, and it may be relatively scanty. Nothing is known with regard to the mode of production of this abnormality, although its general features suggest an endocrine origin. In some instances the onset of the hypertrophic change has been attended by amenorrhœa.

Congenital Abnormalities. The absence of one or both of the mammæ—*amazia*—is of rare occurrence; in some instances it has been associated with a corresponding defect of one or both of the ovaries. *Athelia*, or congenital absence of the nipple, is less uncommon; it usually occurs on both sides. Hypoplasia of the mammæ is met with in association with a similar condition of the ovaries and other parts of the genital system. The term *polymastia* is applied to a condition where there are multiple masses of glandular tissue. Such an accessory mass may or may not possess a nipple; in the former case it is usually rudimentary but sometimes the milk is secreted through it. Supernumerary mammary structures are most frequently met with below the mammæ, although sometimes in other parts. The term *polythelia* signifies the presence of multiple nipples.

Tumours of the Mamma

Simple Tumours. The commonest simple growths are the adenomata, and of these there are several varieties; the hard *fibro-adenoma* on the one hand, and the *cystic adenoma* on the other, representing the extremes. The fibro-adenoma occurs in the form of a well-circumscribed and somewhat elastic rounded mass which may sometimes reach the size of a small orange, though usually it is smaller. It is distinctly encapsulated and is easily shelled out. Two forms of this tumour are usually distinguished according to the mode of growth, namely, the *pericanalicular* and the *intracanalicular*; but both types of growth may be present in the same tumour. In the former (Fig. 569), the epithelial arrangement resembles that in the normal breast, and there is an associated growth of connective tissue and epithelium, though in varying proportion; sometimes the stroma round the acini is myxomatous in character. The type of growth in this tumour corresponds with the normal development of the mamma and the tumour often occurs in the early years of adult life. When the stroma is scanty the term 'adenoma simplex' is sometimes applied in contrast with the commoner fibro-adenoma. In the other type, intracanalicular, there are seen on section numerous curved and branching clefts each side of which is clothed with epithelium (Fig. 570). This structure is really produced by the growth of blunt, rounded projections of fibro-cellular tissue into the lumen of ducts and acini. The covering epithelium keeps pace with the stroma in its growth, and thus the typical structure is produced. Such growths are sometimes multiple and may occur in association with cystic disease, and they then appear to occupy an intermediate position between hyperplasia and true tumours. As Cheatle has shown, the site of origin is inside the elastica of the ducts. Another form of adenoma is one in which there is a formation of numerous small cysts with comparatively scanty stroma—*cystadenoma*. In this type the epithelial cells are larger and more columnar, and not infrequently small papilliform ingrowths form within the cysts. Another variety is that in which a cyst becomes filled with papilliform ingrowths—the ‘ proliferous ’ type ; the cyst may reach a great size, may ulcerate and burst, and a papillomatous mass may project through the skin. Such growths are usually simple in character, but occasionally carcinoma develops, especially in connection with the cystic and proliferous types. The stroma of some adenomata is very cellular, and the term *adenosarcoma* is often applied. Though in the great majority of cases such growths are of simple nature we have seen true sarcoma become superadded (Fig. 571).

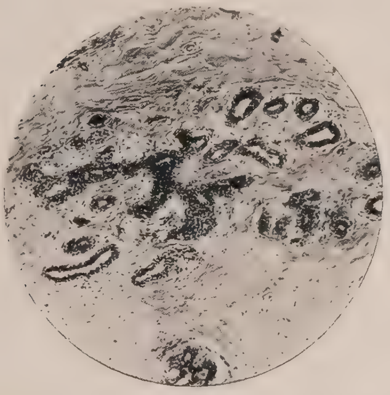

Fig. 569.—Fibro-adenoma of Mamma —pericanalicular type. × 45.

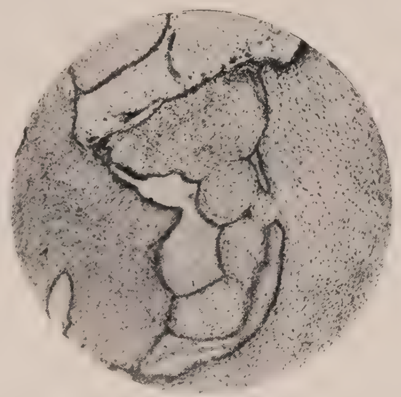

Fig. 570.—Fibro-adenoma of Mamma —intracanalicular type. × 45.

The *duct papilloma* is a rounded and pedunculated form of growth which forms within and distends a duct, often a lacteal sinus. Such a growth shows a branching stroma of varying amount covered by epithelium (Fig. 572). There are usually multiple growths present, but one may be specially noticeable and may reach the size of a cherry or be even larger. Discharge of secretion, and often bleeding from the nipple, may be produced. The occurrence of papilliform ingrowths of different types is very common in cystic disease, and it is then not possible to draw a line between hyperplasia and true tumour growth (p. 902). When multiple small intraduct papillomata are present in the breast the development of carcinoma is in our experience by no means rare, and occasionally this occurs in several foci.

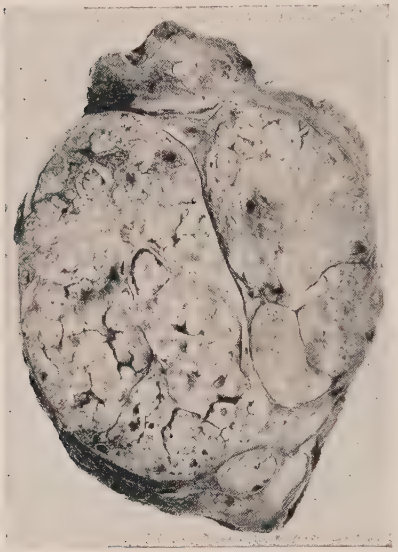

FIG. 571.—Large soft Adenoma of the Mamma; the stroma was very cellular and developed sarcomatous characters. × ½.

Other forms of simple growth, such as pure *fibroma, myxoma, chondroma* and *hæmangioma* may be met with, but they are all of rare occurrence.

Malignant Tumours. *Carcinoma* is by far the commonest malignant growth in the mamma; moreover, it is one of the commonest malignant growths met with in the body. It occurs especially in the later years of adult life, say about 45–65, but is met with both before and after that period. It is somewhat commoner in nulliparæ than in multiparæ, probably owing to its relation to hyperplastic cystic disease which tends to be asssociated with sterility. Several types of mammary carcinoma are met with, but these show the same essential characters.

The *scirrhous* form is much the most frequent, and it tends to produce contraction and indrawing of parts rather than enlargement. It may occur in any part of the breast, though said to be commonest in the upper and outer quadrant, and it forms an indurated area with quite indefinite margins (Fig. 573). When it involves the central parts, the nipple usually becomes retracted, sometimes to a marked degree; especially is this the case in the ‘ atrophic form ’ of scirrhus where the growth remains of small size whilst the contraction is extreme. Such a growth gives a creaking sensation when cut with a knife, and the cut surface shows small yellowish points due to fatty degeneration in the tumour cells; the appearance has been aptly compared to that of an unripe pear. At a late period when the skin becomes involved, ulceration may occur.

There is no situation in which dissemination by the lymphatics is a more striking feature than the breast. The axillary lymphatic glands are early involved and soon become palpable as firm nodules. Extension to the lymphatics in the skin is also of common occurrence. The cancer cells may form numerous small disseminated foci in the skin, or, again, the infiltration may be more diffuse, and the affected skin may become thickened and stiffened ; to this the term 'cancer en cuirasse' is applied by French writers. They use also the phrase 'peau d'orange' to describe a characteristic, though relatively rare, condition in which the skin is somewhat swollen and regularly beset with numerous minute pits. This results from the fine lymphatics being blocked by cancer cells so that the drainage of the skin is obstructed, and œdematous swelling of the skin is produced except at the hair follicles, where it is tacked down to some extent. Extension by the lymphatics occurs deeply along the connective tissue strands to the pectoral fascia, thence into the muscle. Occasionally

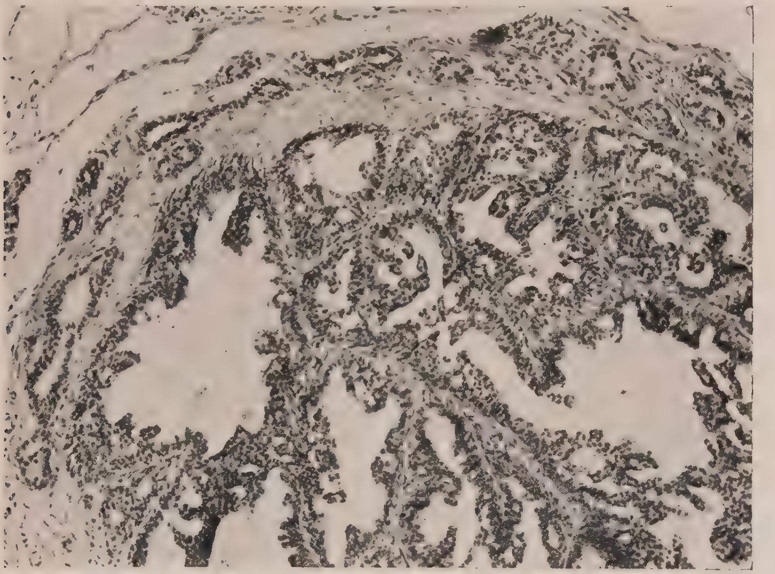

FIG. 572.—Section of Duct Papilloma of Mamma. × 100.

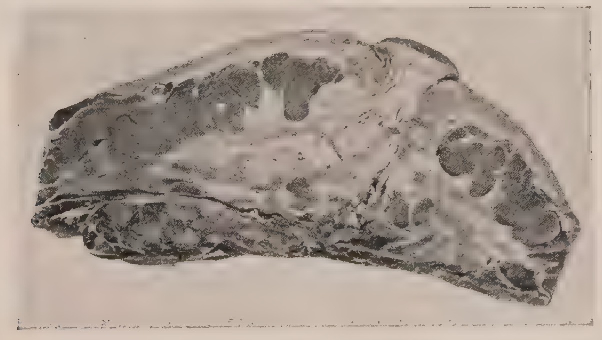

FIG. 573.—Section through Scirrhous Cancer of Breast, showing the irregular character of the growth with indrawing of the Nipple.

also, the pleural cavity may be involved by direct extension. In all these situations there may be nothing visible on naked-eye examination, whilst the microscope reveals the presence of small collections of cancer cells along the lymphatic paths. On this fact is based the principle of the modern method of the treatment of cancer of the breast, viz. to remove as much of the surrounding tissues as possible. It is to be noted that this widespread lymphatic dissemination of the growth occurs with the atrophic as well as with the more rapidly growing forms. In fact, there is an even greater likelihood of secondary growths in the former, as, owing to the insidious nature of the growth, a longer time is apt to elapse before attention is directed to the condition. Ultimately, cancer cells may gain access to the blood stream and secondary growths form in internal organs, and especially in the bones.

Cancer of the soft or *encephaloid* variety also occurs, but is less common than the scirrhous. It may form a large mass or masses with ill-defined margin, and the tissue is somewhat soft and often necrotic in places; hæmorrhage is not uncommon and extensive destructive change involving the skin may follow. On microscopic examination, the stroma is found to be comparatively scanty, whilst the cancer cells are in large collections and often show marked aberration in their characters (Fig. 144). An extreme variety of encephaloid cancer is the '*acute type*' occurring during pregnancy or lactation. The growth is attended with hyperæmia and heat, and a certain amount of pain is fairly common; sometimes there is also some pyrexia. It is of high malignancy in every respect.

In the great majority of cases of cancer of the breast the cells are quite irregularly arranged in alveoli and are of the spheroidal type and quite anaplastic (Fig. 152). In a proportion of cases, however, the cells have not entirely lost their polarity and have a tendency to be arranged at places in acinus-like fashion. The cells may be of columnar form and the growth resembles an adenocarcinoma as ordinarily met with; the same applies to carcinoma within ducts before it has broken through. There is, however, another form to which the term 'cribriform carcinoma' may be suitably applied. It is composed of masses of closely applied epithelial cells, amongst which are small circular spaces, the contents of which are often mucoid (Fig. 574). Such a growth may be confined to the ducts or it may have broken through into the tissue spaces. In the latter case the cribriform type may be retained or the growth may be an ordinary scirrhus. I have found this form of growth of service in tracing the evolution of carcinoma, as it forms a link between the preceding hyperplastic changes and ordinary anaplastic cancer. Adenocarcinoma and cribriform carcinoma may be a little less malignant than the ordinary anaplastic types, but the difference is not marked.

Mucoid or '*colloid*' cancer is a tumour relatively uncommon, though areas of mucoid change are not infrequent in ordinary carcinoma. When mucoid change is general the growth is usually somewhat bulky and of characteristic translucent appearance. It presents the usual invasive characters but on the whole is less malignant than the other forms, and secondary growths in the axillary lymphatic glands are somewhat late in appearance. To this, however, there are exceptions. Occasionally the stroma of a cancer undergoes very extensive mucoid softening, and then the term *carcinoma myxomatodes* has been applied (Fig. 156). Lastly, it may be mentioned that areas of *epitheliomatous* growth may be met with in an ordinary cancer, apparently the result of metaplasia. The two types of growth may infiltrate side by side and the secondary tumours in the lymphatic glands also may be of mixed character.

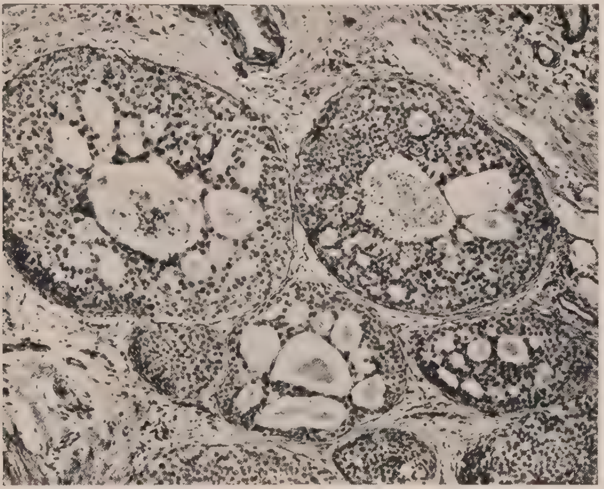

FIG. 574.—' Cribriform carcinoma ', showing masses of cancer cells among which are small circular spaces. The growth is still contained within ducts. × 75.

Intraduct Carcinoma. This term is applied to a condition in which there is malignant proliferation of epithelial cells within the ducts of the mamma ; it is simply a carcinoma which has not broken through the walls of the ducts. The condition in the larger ducts can often be recognised with the naked eye, but more readily with the aid of a lens, since the ducts are filled with cylindrical masses of cells, which can sometimes be expressed as small worm-like structures ; the term ' comedo carcinoma ' is then often applied. The disease may be fairly localised or it may involve the ducts over considerable areas, and it is usually attended by a certain amount of overgrowth of connective tissue leading to induration. On microscopic examination, the cells are seen to be rounded or somewhat irregular in form and to have a vesicular and often hyperchromatic nucleus ;

aberrant types also may be present (Figs. 575, 579). There is in some cases a tendency to gland-like or cribriform arrangement of the cells (Fig. 574). The disease is one of slowly spreading character and may last a long time without breaking through into the tissue spaces. At places the cancer cells may undergo degeneration and retrogression, and obliteration of the ducts is not infrequent; such a process of healing, however, occurs only locally. A corresponding malignant change may occur within acini-*intra-acinous* carcinoma. Thus groups of acini may be filled with cancer cells without any break-through for a time (Fig. 576).

Intraduct carcinoma is a very common type of lesion at a relatively early age—before the 'cancer age.' The proliferating cells may, as we have said, break through the walls of the ducts and give rise to an infiltrating carcinoma. When this occurs the growth is of the usual order of malignancy. On the other hand, when the disease is present in the ducts of the nipple, the cells may spread to the epidermis and infiltrate it, giving rise to the condition of Paget's disease.

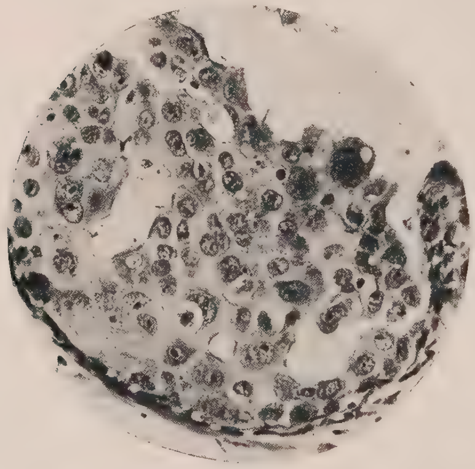
FIG. 575 —Section of Intraduct Carcinoma of Mamma showing collections of Cancer Cells of characteristic appearance lying in the Lumen. × 250.

I have studied over a long period the much disputed subject of the relation of hyperplastic cystic disease and intraduct carcinoma to infiltrating carcinoma and may give a summary of the results. In the first place, in the vast majority of cases of ordinary carcinoma, intraduct carcinoma can be found as an antecedent condition. In a large proportion of these the changes leading up to carcinoma cannot be found, the carcinoma appearing almost as if it started within ducts *de novo*; this question is, however, left an open one. In a small proportion, however, all stages from simple hyperplastic changes to carcinoma have been traced either within ducts or acini, sometimes within both. In such cases, malignancy is not only of multicentric origin but occurs as a gradual process and may affect groups of cells in a diffuse manner. This is strikingly illustrated in the case of the acini, where an intra-acinous carcinoma of considerable extent may develop before the break-through occurs (Fig. 576). The changes found indicate that the carcinoma is the final result of some growth-stimulating agent like a hormone or other chemical agent. I have found no evidence of a dual causation—an agent causing hyperplasia and then another agent such as a virus acting focally and causing malignancy.

Paget's Disease of the Nipple. In this condition, first described by Sir James Paget in 1874, the surface of the nipple in whole or in part becomes reddened, more or less raw or excoriated, and has a florid eczematous appearance. Its tissue may be increased in consistence and there is a certain amount of oozing of clear viscid exudate. Paget noted that the condition may persist for years and that thereafter carcinoma of the mamma often develops. Further, when such a malignant growth appears it is frequently in the substance of the mamma and separated from the nipple by an interval of apparently healthy tissue.

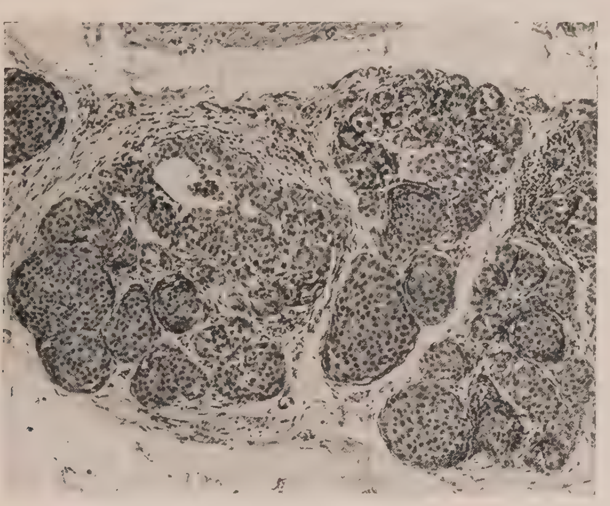

FIG. 576.—Intra-acinous carcinoma, showing groups of acini filled with anaplastic cancer cells without any break-through into tissue spaces. × 75.

Within the epidermis of the affected area the characteristic feature is the presence of peculiar structures known as ' Paget cells,' and with regard to the nature of these there has been much controversy. They occur singly or in groups and are most abundant in the deeper layers of the epidermis, where they may form blunt processes projecting into the connective tissue of the corium (Fig. 577). When they are actively growing they are large, rounded or oval, with vesicular nuclei which are often hyperchromatic and contain large nucleoli. They have in short the appearance of cells of a glandular carcinoma of undifferentiated type. They displace the surrounding cells of the rete Malpighii, which become drawn out or flattened between them

(Fig. 578). Usually, however, many of the Paget cells are undergoing retrogression and when, as is sometimes the case, they are nearly all in this condition, it would be impossible to decide as to their nature. Their nuclei become irregular and pyknotic, whilst the protoplasm has

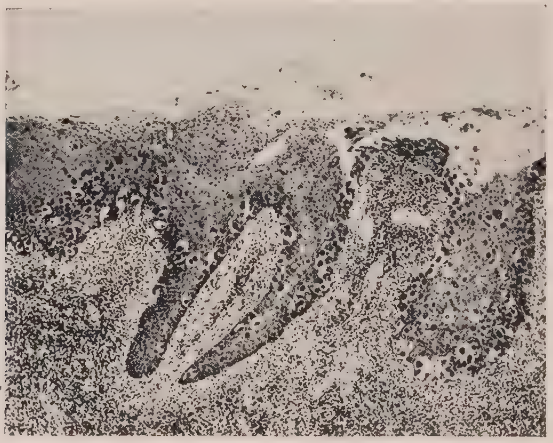

Fig. 577.—Section through Nipple in Paget's Disease, showing scattered Paget cells in deeper part of epidermis.

Note marked cellular infiltration of cutis. × 60.

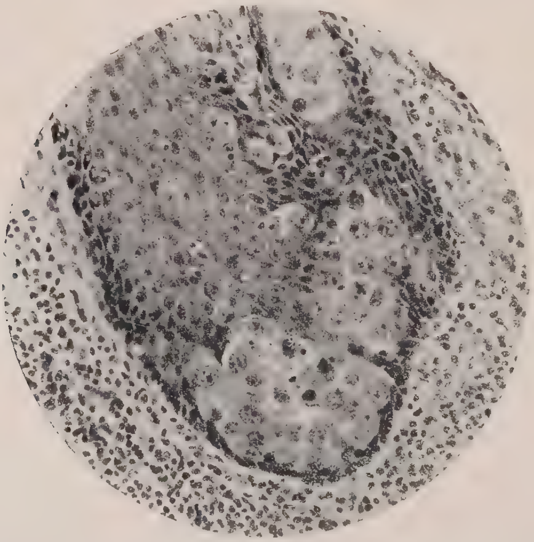

Fig. 578.—Paget's Disease of Nipple. Process of epidermis invaded by cancer cells—'Paget cells.' The cells are specially well preserved and show a marked contrast to the epidermal cells which are being stretched and atrophied. × 200.

a somewhat shrivelled appearance, and the individual cells are sometimes enclosed by a capsule-like structure resulting from condensation of the substance of the surrounding epithelium. It is cells in this condition which gave rise to the opinion once held that they are psorosperms. The cells do not grow into the underlying connective tissue but the latter shows reactive changes—infiltration of plasma cells, etc., new formation of capillaries, congestion with a serous exudate. In this way the characteristic appearance of the nipple results.

Within the epidermis the Paget cells meet with considerable resistance to their growth and hence degenerative appearances often result. We have never seen a case of Paget's disease without intraduct carcinoma being present in the ducts of the nipple (Fig. 579) and in many instances we have traced direct continuity between the cells within the ducts and those infiltrating the epidermis. According to this view, both Paget's disease and ordinary carcinoma of the breast are possible sequels of intraduct carcinoma; neither of these two lesions is related to the other as cause or effect. From the clinical point of view the presence of Paget's disease may be taken as indicating that intraduct carcinoma is present in the ducts of the nipple, that a similar condition of the ducts may be present also in the mamma, and that accordingly there is the likelihood of the development of ordinary carcinoma. Whether the Paget lesion or the cancer in the substance of the breast comes first simply depends on the site of the ducts affected with the malignant disease. The former usually appears first as a clinical condition, but in several cases of infiltrating carcinoma we have found the intraduct carcinoma to have just reached the epidermis or to be on the point of reaching it.

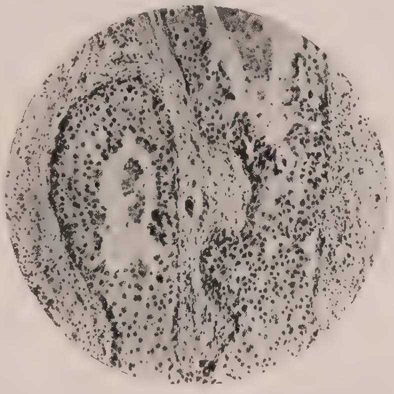

FIG. 579.—Section through Nipple in Paget's Disease, showing malignant proliferation of Epithelium within Ducts—Intraduct Cancer. × 60.

Primary growths of the epidermis are occasionally met with, the cells of which spread intra-epidermally and do not invade the subjacent tissue. Such growths have been observed in the skin of various parts of the body, and are of very rare occurrence. We cannot entirely exclude the possibility that such a growth may originate in the epidermis of the nipple; in this event the appearances of Paget's disease might result. We have personally seen only one case of this kind, and the lesion was in the male breast. We consider that the typical Paget's disease is ordinarily caused in the manner which we have described above.

It is to be noted that true epithelioma of the nipple is sometimes met with and is usually of a chronic nature. Melanotic growth, possibly carcinoma, occasionally originates from the pigmented cells of the areola.

Sarcoma of the breast is relatively uncommon, constituting only a small percentage of the malignant growths ; it occasionally develops in connection with large cellular adenomas. It is usually of the spindle-cell type, though sometimes round-cell and mixed-cell varieties are met with. They present the same general features as elsewhere (Fig. 580).

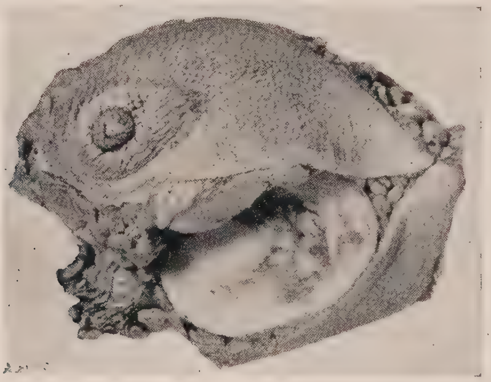

Fig. 580.—Sarcoma of Mamma, shown on section.

It may here be added that hyperplastic disease and tumours of the *male breast* are very rare as compared with those of the female breast, but correspond with them in their general characters. Small fibro-adenomata, in which duct epithelium is chiefly concerned, are occasionally met with. Carcinoma occasionally occurs and is usually slowly growing and not infrequently of adenocarcinomatous type.

CHAPTER XX

THE ENDOCRINE GLANDS [1]

Introductory. Many facts have now been established which show the intimate relationships which abnormal states of these organs have to conditions of disease ; nevertheless, our knowledge with regard to numerous points is still at a comparatively early stage. In many instances the secretion of an endocrine gland has manifold properties and a widespread influence on various parts of the body, and thus a disturbance of the functions of the gland may produce a complicated picture. The chief changes in disease now recognised are the result mainly of increased formation of secretion due to hyperfunction, on the one hand, or of deficiency of secretion due to hypofunction, on the other. There is also the possibility that a secretion may be altered in character, the condition being then called dysfunction, but with regard to this change there is no definite knowledge. Further, certain endocrine glands exert a restraining or antagonistic action on one another, and the normal state results from a balance of their activities ; this is well exemplified in the case of carbohydrate metabolism. When we consider any one endocrine gland, it is found that its action is chiefly in restraining or stimulating vital processes, or, to speak generally, we may say that it exerts a regulating influence. The vital processes thus controlled by internal secretions are various, but may be said to be concerned both with the growth of the body and with metabolism. For example, *growth and development* are known to be controlled by the thyroid, the anterior lobe of the pituitary and the gonads ; and marked abnormality occurs when the secretion of either of these is deficient or absent. Overgrowth resulting from hyperfunction is less frequently seen, but a striking example is presented by acromegaly produced by hyperactivity of the anterior lobe of the pituitary, as will be described below. In such cases the growth of bone is involved in a striking manner, and it is possible that various diseases of bones whose nature is still obscure may be due to abnormal states of the endocrine glands.

The *reproductive function* is intimately related to the endocrine glands, especially to the thyroid, adrenals and the pituitary, and may pass into a state of inactivity when the secretion of these glands is deficient. A relationship exists also between the adrenal cortex and the genital glands, and curious abnormalities are sometimes met with in hyperplasia of the former. As a regulator of *general metabolic processes* the thyroid constitutes the outstanding example. It has now been established both by experimental methods and by observations on conditions of disease, that its secretion in excess raises the normal basal metabolism, whilst deficiency has the contrary effect. There is evidence also that the secretion of the chromaffin system has a similar action, though it is relatively slight. Several of the endocrine glands exert, as we have indicated, a co-ordinated action on the *metabolism of carbohydrates*. The internal secretion of the pancreas is essential for the storage and utilisation of sugar, and defect of its secretion, *insulin*, leads to marked hyperglycæmia and glycosuria, that is, to diabetes. On the other hand, the secretions of the thyroid, of the chromaffin system, and apparently also that of the posterior lobe of the pituitary, act in mobilising sugar, and accordingly excess of secretion leads to glycosuria. In this respect there may be said to be an antagonistic action between the pancreas and other endocrine glands.

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[1] For details the student is referred to *Recent Advances in Endocrinology*, by A. T. Cameron, 4th edition, London, 1940 ; or *The Diseases of the Endocrine Glands*, by H. Zondek, 3rd edit., London, 1935.

It has now been shown that *calcium metabolism* also is controlled by internal secretions. Removal of the parathyroids, for instance, is followed by a fall in the amount of calcium present in the blood and decreased excretion. On the other hand, parathyroid hyperfunction as met with in association with adenomata of the gland, leads to withdrawal of the calcium from the bones and hypercalcæmia. Injection of the parathyroid hormone has a like effect.

Again, interaction between the *nervous system* and the various endocrine glands is doubtless of great importance. The nervous connections between the hypothalamic nuclei, to be referred to below, afford a striking example of this. Deficiency of thyroid secretion acts as a depressant on nervous activity, including cerebration, and when it occurs in early life leads to deficient mental development ; and the same holds to a certain extent with regard to hypofunction of the anterior lobe of the hypophysis. Hyperthyroidism, on the other hand, leads to excitability and nervous instability. It is quite possible that disordered endocrine activity and even structural changes may be started through the nervous system. Exophthalmic goitre, for example, may possibly be produced in this way. It is known that the discharge of internal secretions, for example, of adrenalin, is influenced by the nervous system, and furthermore, adrenalin in its turn appears to act largely by its action on the fibres of the sympathetic.

In addition to there being in some instances a balanced action of internal secretions, the endocrine glands act on one another, and removal of one may be followed by structural changes in the others. In disease several may be affected together, the disease being then spoken of as ‘ polyglandular ’ ; and it may sometimes be impossible to say whether there is a primary lesion in one, or whether several have been affected by a common cause. The enlargement of one gland following the removal of another is sometimes described as compensatory, but it must not be assumed that the enlarged gland takes on the functions of the one which has been lost. The various internal secretions rather appear to be specific to the several glands, and there is little evidence that the loss of one can be vicariously made good by the hyperactivity in another. Various syndromes of endocrine disease have been described and their number is constantly being added to, but it is often not possible to say in which gland the primary lesion has been and, as a rule, the real etiology is unknown. The facts which we have given are merely examples of disturbance of endocrine disturbance but will serve to illustrate the extent and complexity of the subject.

A vast amount of experimental work has been done on this subject in recent years and it is not possible to give here even a résumé, especially as many questions are still *sub judice*. In the following account we shall deal with the chief disorders of function and structure met with in human disease, and the experimental results referred to will be mainly those bearing directly upon the pathological states under consideration.

The pituitary will be considered first as it is now generally regarded as the centre of the endocrine system. This is justifiable in view of its position and its nervous connections with the nuclei at the base of the brain. The number of hormones produced by it with their specific effects, and the fact that removal of the pituitary produces atrophic changes in the other endocrine glands, are also in accordance with this view. It must be recognised, however, that there is also reciprocal action of the various glands on the pituitary and that the initial lesion of a syndrome may be in any of them.

THE PITUITARY[1]

Introductory. Our knowledge of the important functions of the pituitary as an endocrine gland may be said to start with the work of Marie, published in 1886, who showed that the peculiar state called by him ‘ acromegaly ’ was associated with enlargement of the gland. Since that time further observations and experimental work with regard to the effects of extirpation, in which Cushing was the pioneer, have supplied much knowledge of importance. As in the case of other endocrine glands, the action of extracts has been extensively studied and various hormones have come to be recognised.

It is unnecessary here to describe the structure of the pituitary, but it is important to recognise that its complexity provides a basis for the diversity of its functional activities. So far as dual constitution is concerned, there is a certain analogy with the adrenals. The anterior lobe is essentially of glandular structure and of entodermic origin, while the posterior represents a downgrowth from the diencephalon. Not only, however, have we to deal with anterior and posterior lobes and pars intermedia, but also with the different kinds of cells which constitute their structure. Thus in the anterior lobe we have cells devoid of granules or chromophobe cells which constitute fully 50 per cent. of the total number, and also chromophile cells, the latter being of two types, namely, eosinophile or alpha cells and basophile cells or beta cells. The basophile cells usually number a little more than 10 per cent. ; the eosinophile cells occupy an intermediate position with a percentage a little under 40. Whether the chromophobe cells represent an early stage and develop into the cells of the two chromophile classes is not certain, though for this there is evidence, but it is important to note at this stage that there is no evidence that they produce a hormone.

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[1] For a detailed account see *The Pituitary Gland*, by W. Timme, A. M. Frantz and C. C. Hare, Baltimore, 1938.

The number of pituitary hormones described by various authorities varies greatly. They have not yet been obtained in a pure form and, as Collip suggests, some of them may be split products of larger molecules. One may be justified, however, in provisionally stating that the chief varieties are, (1) a growth-stimulating hormone, (2) gonadotropic hormones, (3) a thyrotropic hormone, (4) an adrenotropic hormone, (5) a lactogenic hormone. Of these, the growth-stimulating and the gonadotropic hormones are prominently concerned in human disease. They are both products of the anterior lobe, the first being formed by the eosinophile cells and the latter in all probability by the basophile cells.

Growth-stimulating Hormone. Cushing showed that the extirpation of a considerable part of the anterior lobe, along with the posterior lobe, produces in puppies a sort of infantilism. The animals remain small owing to interference with osseous growth, the sexual glands fail to develop, and there is a marked adiposity accompanied by increased tolerance of sugar. The temperature tends to be subnormal and the animals are stupid. The accumulation of fat is now believed to be due to injury to the tuber cinereum or adjacent parts. In adult animals the lesion mentioned causes corresponding effects, with the exception that the effect on the osseous system is not evident, and that the change in the sexual glands is of a retrogressive nature. Experiments in which the whole gland is removed seemed to show that a fatal result necessarily follows, a sort of acute cachexia developing. It was, however, established, notably by the work of Dandy and Reichert, that the gland is not essential to life. They removed the whole gland from puppies and a considerable number of the animals survived for varying periods. It is noteworthy that, in a fairly large proportion, only the effects on growth and sexual development followed. Complete extirpation has since been extensively used as a method of enquiry.

The functions of the pituitary have been investigated also from the other point of view, viz. by the injection of extracts of the lobes of the gland—by substitution therapy. For a long time attempts to promote growth by anterior lobe extracts were unsuccessful, but later Evans obtained striking positive results, which have since been confirmed. By repeated intraperitoneal injection in rats of extracts of the anterior lobe of the ox, he found that marked increase of the bony skeleton and other parts followed. This occurred in adults as well as in young animals, but in the former the characteristic changes of acromegaly did not occur in the skeleton—only giantism (*vide infra*). This is apparently due to the fact that in the rat the epiphyseal lines of the bones do not become ossified. Corresponding results have also been obtained in puppies by injections of anterior lobe extract, and it is interesting that in them some of the features of acromegaly have been reproduced. By these various methods the relation of the anterior lobe to body growth has been completely established. The source of the growth-stimulating hormone is the eosinophile cells of the anterior lobe. The results are in full agreement with those of human pathology, to be presently described.

Gonadotropic Hormones. In connection with the action of the pituitary on the gonads, there are two phenomena to be considered, namely, (*a*) the establishment of sexual maturity and (*b*) the reproductive cycle. As already stated, excision of the anterior lobe has a depressing effect on the gonads, inhibition of development in young animals and the production of atrophic changes in adults. The production of the opposite effect, that of stimulation, has also been obtained. Transplantation of anterior lobe tissue to immature female rats and mice leads to precocious sexual maturity (Smith and Evans ; Zondek and Ascheim). The action is directly on the gonads and through them on other parts of the reproductive system. Similar results have been obtained by anterior lobe extracts. Corresponding effects occur in male animals.

Zondek and Ascheim, as the result of further analysis, came to the conclusion that the anterior lobe produces two hormones with action on the ovaries, which they called Prolan A and Prolan B. (This view was for a time called in question, but it seems now to be accepted.) Prolan A regulates the growth of the Graafian follicle and ovulation ; and the follicle in its turn to produce a hormone œstrone or theelin which stimulates the reparative changes in the endometrium after menstruation (p. 870). Prolan A also stimulates male germ cells. Prolan B, on the other hand, controls lutein formation, the corpus luteum in its turn producing a hormone which leads to the premenstrual changes in the endometrium and which is also inhibitory on ovulation. There is very strong evidence that these hormones are produced by the basophil cells and that increase in the number of these indicates more active formation of the principles.

The Ascheim-Zondek test for pregnancy depends upon the presence of a definite substance in the urine in pregnancy. When the urine is injected into immature female mice and rats the ovaries become congested and swollen, and small hæmorrhages appear on their surface; lutein formation occurs in the Graafian follicles. The substance concerned was believed to be prolan B formed in excess by the anterior lobe. It has now, however, been demonstrated that it differs from the anterior pituitary sex hormones in certain respects and that it corresponds in its characters with a hormone obtained by Collip and his co-workers from the placenta; this is often known as the A-P-L principle (anterior-pituitary-like). It is formed by the fœtal part of the placenta, the fœtal ectoderm thus having the properties of an endocrine gland. Differences have been established between the pituitary sex hormone and the A-P-L principle; for instance, the latter does not remove the retrogressive effects on the gonads brought about by hypophysectomy. The A-P-L principle appears to act through the pituitary in association with the sex hormones formed by it; it enhances the effect of the latter in hypophysectomised dogs. This view with regard to the origin from the placenta of the reacting body in the urine agrees better than the old with the fact that retained placental tissue, chorion-epithelioma and hydatidiform mole give a positive result with the Ascheim-Zondek test for pregnancy. It may be added that Collip has found that the placenta produces another gonadotropic hormone, emmenin, which acts on oral administration, and is also a source of œstrone.

Some of these statements may require modification but it is quite clear that there is a remarkable interdependence of the pituitary and reproductive organs. It is possible that certain abnormalities of the ovaries and mammæ, such as cystic change, may depend upon pituitary abnormality, but with regard to this, information is wanting. It may be added that mutual action exists between the pituitary and the various other endocrine glands. When multiple lesions are present it may be impossible to say which is primary.

With regard to the other anterior lobe hormones, *thyrotropic, adrenotropic and lactogenic*, it is unnecessary to speak in detail. They have essentially a stimulating effect on the corresponding organ and this has been established in the case of all by methods corresponding to those described. It is an interesting fact that the thyrotropic hormone produces hyperplastic changes in the thyroid epithelium not unlike those in the exophthalmic goitre, though these are not of permanent character. The close relationship between the pituitary and the adrenals is indicated in the accounts of pituitary basophilism and of cortical tumours of the adrenals (pp. 923, 963). Lactation in the rat is stopped by excision of the pituitary and is restored by injection of anterior lobe extract. The sources of these hormones has not been definitely established, but there is evidence that the thyrotropic like the growth-stimulating hormone is formed by the eosinophile cells and that the adrentropic like the gonadotropic is formed by the basophile cells.

The earlier experimental results showed that the extract of the *posterior lobe*, pituitrin, when injected into normal animals causes certain definite effects. But it is now known that there are two hormones; one, *pitressin* or *vasopressin*, has certain resemblances to adrenine in its action, raising the blood pressure and having in sugar metabolism an action opposite to that of insulin. It has also an anti-diuretic effect on normal animals in sufficient dose, and deficiency of it is an essential feature in diabetes insipidus (p. 926). The other hormone, *oxytocin*, has a stimulating effect on the uterine muscle and is supposed to be concerned in stimulating uterine contraction at the end of pregnancy. It is to be noted that removal of the posterior lobe leads to no definite effects provided that the hypothalamic region and the anterior lobe are not injured. On the other hand deficiency of vasopressin is concerned in the production of diabetes insipidus, as will be described below. This apparent discrepancy still requires elucidation. The source of the posterior lobe hormones is still matter of dispute. By some observers they are ascribed to the pituicytes of the pars nervosa, by others to the epithelium of the pars intermedia.

We shall give an account of the conditions depending upon excess and deficiency of secretion respectively, but it must be recognised that some of the views are rather of the nature of hypotheses and may have to be modified. It is to be recognised also that the interpretation of the lesions and symptoms of pituitary disease is attended with special difficulty. For not only are there two essentially different lobes of the pituitary, but, owing to the relation of the gland to the bone, enlargement of one may press on the other, and thus hyperactivity of one may be associated with hypoactivity of the other. The facts observed indicate too that a state of hyperactivity of one portion may be succeeded by one of hypoactivity, as will be illustrated below. Furthermore, a pituitary tumour may affect the hypothalamic region, and conversely a suprasellar growth may produce pressure effects on the pituitary. The problem presented is often one of great complexity.

Pituitary Hyperfunction

(1) **Acromegaly.** The term originally applied by Marie, means enlargement of the extremities, and the condition may be attributed to hyperactivity of the anterior lobe with excessive formation of secretion. A disordered secretion has been suggested in explanation, but of such a condition there is nothing definitely known. The hands and feet are increased in size, especially in width, and the former have been described as spade-like; the increase is mainly on the part of the soft tissues, though thickening of bone may be present at a later stage. The face is enlarged, especially the nose, which is widened; and the lower jaw is lengthened and its angle is widened, so that the teeth project beyond those of the upper jaw. The lips become thickened and there is enlargement of the tongue. The skin is thickened and sometimes warty, and the hair coarse and wiry. In the skeleton

generally there tends to be an increase of the bony prominences, and there may be roughening of the surface of the bones. Kyphosis is often present. The sternum is increased in size and the thoracic cavity is enlarged. Although the changes occur after normal ossification is completed, a slight increase in height has been noticed in some cases. The effects of the growth-promoting hormone are seen also in the internal organs, there being enlargement of the liver, kidneys, etc.—a condition of visceral splanchnomegaly. Hyperplastic changes have been found also in the thyroid, parathyroids and adrenal cortex, while in cases of deficiency the opposite state is present (Cushing and Davidoff).

Such is a general summary of the chief structural changes, and they may be said to represent an irregular overgrowth both of bone and the soft tissues. General lassitude, muscular weakness, slowness of speech, etc., are common symptoms of acromegaly, and these increase during the progress of the disease. At first diminished sugar tolerance may be noted, sometimes glycosuria, but later increased sugar tolerance is present. In early stages there may be some evidence of stimulation of sexual functions, but this is soon followed by depression, attended by impotence in the male, amenorrhœa in the female, etc. This is in accord with what has been mentioned above as to the effects on the gonads of injections of anterior lobe extract in rats. Symptoms may be produced by mechanical pressure of the pituitary tumour which is often present; another effect is implication of the inner halves of the optic nerves with temporal hemianopsia as a result. Choked disc and other signs of intracranial pressure may be produced when the hypophyseal growth is large, and occasionally blindness results. Although acromegaly in its fully developed form is rare, slighter degrees of the condition are more frequently met with.

(2) **Giantism.** Hyperactivity of the anterior lobe before ossification is completed, is now recognised as the cause of giantism. There is excessive growth at the epiphyseal lines and this may be prolonged beyond the normal period. The growth is precocious and of proportionate character: ultimately a height of over eight feet may be reached. In some cases, the effects of hyperactivity persist after the period of normal growth and some of the features of acromegaly may be superadded. At an early stage there may be abnormally great muscular power and energy, which are usually attended by precocious sexual development and libido; but at a later stage these are replaced by muscular feebleness, impotence, etc., along with mental impairment. There is often glycosuria at first, but later increased sugar tolerance may develop.

The lesion associated with acromegaly is an enlargement of the anterior lobe, usually described as an adenoma, though occasionally the growth has shown aberrant characters. Sometimes a cyst or cysts have been found, and such an occurrence but represents a later stage, which may be associated with insufficiency. The tumour may reach a considerable size, giving rise to enlargement of the sella as can be found on X-ray examination and also growing upwards and leading to pressure on the optic chiasma and overlying parts of the brain. Benda was the first to point out that in the adenoma or hyperplasia of the anterior lobe associated with acromegaly, it is the chromophile cells of the eosinophile type which are increased, and his observation has been since fully confirmed. In fact, this has been so uniformly the case in a long series of instances, that it may safely be stated that the form of hyperactivity which causes the changes in structure and function in acromegaly is on the part of the eosinophile cells. A similar statement as to the cells concerned applies to the condition of giantism, but here the lesion is more frequently hyperplasia than actual adenoma. The effects on the sexual functions, at first hyperactivity then hypoactivity, may be due to an initial stimulating effect of the adenoma on the basophile cells followed by destruction. Certainly in most cases of acromegaly the growth is practically a pure eosinophile adenoma. The close association between stimulation of growth and stimulation of gonads is, however, noteworthy.

(3) **Pituitary Basophilism.** This condition was first described by Cushing who collected a number of cases where a group of changes was associated with a basophile adenoma. These included painful adiposity of the body, often accompanied by striæ on the skin of the abdomen, excessive growth of hair (hypertrichosis) of the masculine type, impairment of sexual functions—amenorrhœa or impotence—high blood pressure and glycosuria. An element akin to virilism appears to be present. The syndrome is now conveniently called ‘ basophilism.’ A remarkable feature is the small size of the pituitary tumour which is not infrequently associated with the syndrome mentioned.

The original view was that the syndrome was the result of hyperfunction of the cells of the adenoma, but doubt arose as to this. There was the fact that many of the symptoms might be associated with hyperplasia or an adenoma of the adrenal cortex, or with a tumour of the thymus. And the further fact was established that in such cases there might be no increase in the number of the basophile cells of the pituitary. Again, in some cases a basophile adenoma might be found without accompanying signs of basophilism. The original view did not correspond with facts and the position was obscure. An important contribution to the subject was made by Crooke. He examined the pituitary in the three conditions in which basophilism is present, viz. basophile adenoma of the pituitary, tumour or hyperplasia of the adrenal cortex and tumour of the thymus, and found that in all three conditions there was present a peculiar hyaline change in the basophile cells of the pituitary ; this was the only lesion common to the three conditions mentioned. He considers that the change is probably an expression of altered physiological activity and not an indication of cell degeneration. Of a large number of other conditions in which the syndrome was absent, the change was found in only a few, and in them it was of slight degree. Crooke's results have been confirmed by those of others. The hyalinisation of the basophile cells apparently represents a state of functional activity but its origin and real significance are not yet known.

Pituitary Hypofunction

Cases of this state occur both in early and late life. As a group they represent mainly the effects of deficiency of the growth hormones and the gonadotropic hormones. In one type a condition of adiposity is present in addition and this is considered to be the result of a lesion outside the pituitary. In the other there is no such tendency to accumulation of fat. As can readily be understood, the deficiency may be brought about either by a lesion within the pituitary itself, tumour or destructive lesion, or by pressure from a growth outside. The pituitary defect *per se* is often complicated by the effects of lesions in the hypothalamic region. Various syndromes have been described but in many the underlying structural change has not been determined. We shall give a few of the main facts established.

Simmonds's Disease. This is the commonest and most important example of anterior lobe hypofunction. Simmonds described the lesion as being of a necrotic nature produced by vascular disturbance, and he observed such a lesion as a post-partum condition. Since then a similar syndrome has been described in cases of fibrosis, tumours and cysts involving the anterior lobe. The term *pituitary cahexia* has sometimes been used as a synonym for the resulting syndrome. Sheehan has recently made a very important contribution to the subject by showing that it is not an uncommon post-partum occurrence and describing both pathological and clinical features. He finds that the original lesion is necrosis in varying degree of the anterior lobe, this occurring especially when labour has been complicated by collapse or shock, notably when accompanied by hæmorrhage. The necrosis is the result of thrombosis, and it is followed by absorption of the necrotic tissue and by fibrosis, with consequent shrinking. It is quite likely that cases of fibrosis recorded by others have been produced in this way. The subsequent functional changes represent the results of anterior lobe damage. During the puerperium there is absence of lactation and this is succeeded by important effects on the reproductive system. Thus there occur amenorrhœa, absence of libido, atrophy of the ovaries and uterus, and disappearance of the pubic and axillary hair. The basal metabolism rate and blood pressure tend to be lowered and there is often a degree of hypochromic anæmia. The patients show lassitude, asthenia and sensitiveness to cold. There are also atrophic changes in the adrenal cortex, thyroid and parathyroids. At an early stage there is indication of premature senility or progeria, but, later, symptoms of myxœdema develop and gradually become more and more prominent ; the latter is apparently due to the atrophic condition of the thyroid. No doubt as in the case of other diseases, milder forms of the condition will be found to be commoner than is supposed.

In this disease we have accordingly a striking example of the diminution of activities of the anterior lobe, and the merit of Sheehan's work has been to relate this to a definite lesion of definite etiology. It may be noted that a number of the symptoms described may be present in other conditions apart from a pituitary lesion. Some of them occur in the condition known as *anorexia nervosa*, which is of psycho-neurotic origin, but it seems to us that the study of clinical symptoms alone and the formation of so-called syndromes without knowledge of structural changes, is more likely to retard than to advance progress in this department.

Fröhlich's Syndrome. The condition known by this name was described by Fröhlich in 1901, or *dystrophia adiposo-genitalis*, closely corresponds with the results obtained experimentally by Cushing in the case of puppies. Children affected by this dystrophy are small, of infantile habit and abnormally fat, and the sexual glands remain undeveloped ; there is also increased sugar tolerance. Boys assume some of the female characters, the hips are wide and there is an accumulation of fat in the mammæ and over the buttocks. Basal metabolism is lowered and the temperature tends to be subnormal. The results of operations and post-mortem examinations have been to show that while occasionally an adenoma has been present, in the great majority of cases the lesion has been a growth overlying the pituitary and compressing it. When a pituitary adenoma has been present, it has been of the chromophobe type, never eosinophile. Compression by supersellar tumour may clearly affect both the pituitary and the parts above it, and thus give rise to the deficiency complex mentioned. Of the tumours bringing about this result the commonest are the congenital growths in the region of the infundibulum and derived from the cranio-pharyngeal pouch of Rathke. These contain epithelial elements, are solid, often cystic, and are not infrequently the seat of calcification especially in their periphery ; thus they can often be seen in an X-ray plate. Occasionally bone is formed in the stroma. Further, in some instances the growth has been a meningioma or a glioma, and the Fröhlich syndrome has been observed to result also from severe internal hydrocephalus.

The changes present in Fröhlich's syndrome point to some other factor in addition to deficiency of the secretion of the anterior lobe. Cases also are recorded, however, where there has been interference with osseous growth and the development of the sexual glands, but where accumulation of fat has been absent. In such cases the normal proportions of the body are maintained. Ossification generally is imperfect, and the bones are slender and sometimes fragile ; intelligence is, as a rule, impaired. In extreme examples a condition of dwarfism results. Cases of this nature are now usually known under the title of Lorain-Levi syndrome. Erdheim, who calls the condition *nanosomia pituitaria*, considers that the anterior lobe alone is involved, and that when deficiency in growth is associated with accumulation of fat there is also some injury to the base of the brain.

Other examples of pituitary dwarfism have been described, but until the underlying lesions have been defined we have little knowledge of the real meaning of the syndromes. It is, of course, evident that the characters of the syndromes may depend on a lesion in the anterior or posterior lobe, or in the hypothalamus, or on various combinations of these. In one syndrome, known as the Lawrence-Moon-Biedl, there is evidence that an hereditary influence is concerned, the dwarfism being accompanied by a retinitis pigmentosa and polydactyly. A similar influence is thought to obtain in the Lorain-Levi syndrome. It may be noted that in many cases of pituitary dwarfism no evidence of a tumour has been found on X-ray examination.

Cases with features somewhat similar to those in Fröhlich's disease occur also in adults and are believed to be the result of insufficiency after growth has ceased. Here also there is great accumulation of fat with loss of sexual function—impotence in the male, amenorrhœa and sterility in the female ; there is also increased sugar tolerance. In the male the disposition of the accessory fat may lead to a female configuration. Women are more frequently affected and the increase of fat is sometimes very great, especially over the trunk where it may be somewhat irregularly distributed ; the adipose tissue is often tender or even painful. Cases of the latter type are often spoken of as *adiposis dolorosa* or Dercum's disease, but different conditions have probably been included under this term. It cannot be said at present whether all such cases are due to hypophyseal deficiency, but in many cases of the kind carefully examined, the lesion present has been an adenoma of the chromophobe type, which evidently produces anterior lobe deficiency by replacing the eosinophile cells ; it may also cause effects from pressure on the hypothalamic region. The mechanical results of such an adenoma are the same as those met with in acromegaly, viz. headache, restriction of the field of vision, bitemporal hemianopsia and sometimes blindness.

Diabetes Insipidus. This affection is characterised by persistent failure to concentrate urine and by polyuria. It is attended also by polydypsia and a certain amount of emaciation. The underlying lesion is usually in the hypothalamic region and is of varying nature—tumours, gummata, injuries, etc. ; in some cases it has been post-encephalitic. Persistent polyuria has been produced and studied by experimental lesions in the region mentioned by various observers. The effect does not seem to be definitely related to one particular nucleus. It is now known that a neuro-endocrine mechanism is concerned, consisting of nerve centre in the hypothalamus, a band of non-medullated fibres in the pituitary stalk and the posterior lobe which produces the hormone.

A lesion in the nucleus, or interruption of the fibres by incision or by clamping, results in diabetes insipidus and this, like the disease in the human subject, is relieved by injections of vasopressin. So much is clear but some points have not yet been explained. For example, total extirpation of the pituitary does not produce the condition nor is it met with when the posterior lobe is destroyed by tumour. It has been found too that the presence of a certain amount of functioning anterior lobe is necessary for permanent polyuria (Biggart and Alexander). There is still want of agreement as to the cells concerned in the production of the hormone. There has been a tendency to ascribe this function to the cells of the pars intermedia, but it is held by some that the special cells of the posterior lobe, called pituicytes, are those concerned. This may well be the case seeing that the pituicytes correspond to an extent with the chromaffin cells of the adrenal medulla which produce adrenine.

Tumours

These are of considerable variety but of rare occurrence. As has already been mentioned, enlargement of the hypophysis may be due to an adenomatous growth, and this may be composed mainly of one of the three types of cells, in the anterior lobe—*chromophobe*, *eosinophile*, *basophile*. The frequency of occurrence of the corresponding adenomas is in this order. Occasionally an adenoma assumes malignant characters. There is general agreement that adenomas of the *chromophobe* type do not lead to specific symptoms or evidence of hyperfunction but are usually attended by signs of anterior lobe deficiency. They may also cause effects by pressing on the hypothalamic region. Such growths are, however, rare before adult life, and the results of anterior lobe deficiency in early life are usually produced by the pressure of a growth outside the pituitary. A chromophobe adenoma is composed of masses of round cells of rather indifferent appearance lying in alveolar spaces enclosed by fibrous stroma. It has been shown by Cramer and Horning that prolonged injection of œstrone in mice produces hyperplasia of the chromophobe cells and sometimes an actual adenoma, in which eosinophile and basophile cells are very scanty. This is a very interesting example of the action on the pituitary of the hormone of another endocrine gland. The *eosinophile* adenomas quite clearly show hyperfunction which leads to overgrowth as seen in giantism and also effects on the gonads. Both chromophobe and eosinophile adenomas may reach a considerable size, causing absorption of bone and pressing on the optic chiasma and adjacent parts. The *basophile* adenomas are the rarest type of tumour and are usually of small size.

The commonest growth outside the pituitary and producing anterior lobe deficiency by pressure is one of congenital origin and derived from cells of the cranio-pharyngeal pouch of Rathke, from which the hypophysis is developed ; it is often cystic (p. 925). Cystic tumours or cysts occasionally arise also from the acini of the pars intermedia and may cause atrophy of the rest of the gland. As has been mentioned above, extra-pituitary tumours in the suprasellar region may involve the nuclei of the hypothalamus and lead to disturbances of fat metabolism and also polyuria. Sarcoma may be met with, but it is very rare.

Pineal Gland. What is known with regard to this gland chiefly concerns tumours. Those observed have been of different types but mainly teratoid growths, adenoma or pinealoma, and ganglioneuroma. They have been met with especially in early life ; all are of rare occurrence, especially the last mentioned. Effects are produced by pressure on neighbouring structures ; thus hydrocephalus, ocular paralyses and deafness from implication of the corpora quadrigemina, also cerebellar effects, giddiness, etc., may result. In a number of cases affecting young boys an interesting phenomenon has been the condition of *pubertas praecox*, there being an excessive growth of the body and premature development of the sexual organs accompanied by hirsuties and sometimes obesity. In other cases of pineal tumour such effects have been absent, and further a similar group of changes has been met with in other lesions in the neighbourhood, such as growth in the floor of the third ventricle, hydrocephalus, etc. It is accordingly not possible to say whether the syndrome is really a pineal effect or whether it is the result of disturbance of nerve tracts possibly related to the pituitary. Experimental work on the subject has been unsatisfactory but recently striking results have been announced by Rowntree and others. They have found that the continued injection of pineal extract to rats in successive generations results in retardation of the growth of the body but acceleration of somatic differentiation and of the onset of adolescence. These changes appear in the third generation, and later the result is dwarfism and sexual precocity. These results of the injection of pineal extracts are of interest in relation to those obtained with thymus extracts, as in both cases there is an intensification of effects in successive generations. So far as bodily growth, however, is concerned, the effects are of opposite kinds. Experimental removal of the pineal has as yet given no definite information.

THE THYROID[1]

The most important results of disease of the thyroid depend on absence or deficiency, on the one hand, and excess on the other, of the thyroid secretion ; and these are met with chiefly as the results of atrophic change and hyperplasia of the gland respectively. The results of thyroidectomy for goitre in man, the symptoms associated with atrophic or hypoplastic disease of the gland, and the effects of experimental removal of the gland in animals, are in harmony in showing the important definite effects which the internal secretion of the thyroid has on growth and metabolism. The common occurrence of tetany and other nervous symptoms when the gland was removed in cats and dogs, at first appeared to be in disagreement with the general results, but it is now known that such symptoms of acute nature are due to removal of the parathyroids (p. 953) along

[1] For details see *Diseases of the Thyroid Gland*, by Cecil A. Joll, London, 1932.

with the thyroid. Deficiency of the thyroid secretion in the early years of life leads to imperfect growth of the body generally, especially of the osseous system and the genital glands, and interference with the development of the mental faculties. These effects will be described in connection with sporadic cretinism.

In the adult, the nutritional effects of deficiency are seen in the changes which occur in the cutaneous and other connective tissues, and in the associated atrophy of the hair and other structures of the skin. The nervous system also is profoundly affected, apathy, slowness of cerebration, and sluggishness of nervous response being prominent features. It is to be noted that no known hypertrophic changes of the tissues are produced by hyperactivity of the gland, such as occur in the case of the pituitary. In addition to the effects on growth and the nutrition of the tissues, the thyroid secretion has an equally important influence in promoting metabolism and in various functional activities. The basal metabolism, that is, the number of calories produced by an animal or individual in a fasting condition and at rest, is diminished when the thyroid secretion is deficient; and there is a tendency to subnormal temperature. On the other hand, hyperactivity of the gland raises the basal metabolism, and the injection of thyroid juice or thyroxin in animals has the same effect. Like other endocrine glands, the thyroid is intimately related to carbohydrate metabolism. Diminution of the thyroid secretion leads to an increased tolerance of sugar, so that it is impossible to produce glycosuria by oral administration of glucose, and the effects of adrenalin and other agents which produce glycosuria are much diminished. Conversely, hyperactivity of the thyroid leads to increased mobilisation of sugar and tendency to glycosuria.

The activity of the thyroid secretion is shown to depend on an iodine-containing substance. Baumann in 1895 showed that the thyroid contained a very much larger amount of iodine than any other tissue of the body, and that the iodine existed in combination with a protein to which he gave the name iodo-thyrin. Oswald found that in the colloid material two globulins were present in association, and one of these containing iodine he named iodo-thyro-globulin. Thereafter Kendall isolated in crystalline form an iodine-containing substance which he called thyroxine. Somewhat later Harrington demonstrated the true constitution of thyroxine, and later still, in collaboration with Barger, synthesised it. Thyroxine, an amino-acid, is a condensation product of two molecules of di-iodotyrosine. It contains about 60 per cent. of iodine. The thyroid thus has a store of iodine-containing protein in its colloid, the specific physiological action of which is due to its constituent thyroxine. It has been shown that practically all the iodine of the thyroid is in organic combination.

It has been shown that feeding with thyroid or thyroxine has a remarkable effect in retarding the growth of young animals. In the case of tadpoles there is a decrease in size with premature development of the adult characters, reduction of the tail, etc. This fact which is the basis of what is known as the Gudernatsch test is made use of in investigating the properties of thyroid secretion in different conditions, especially as regards its iodine content.

We shall now give an account of the chief diseases of the thyroid, dealing first with those resulting from deficiency. Of the latter there are two main examples—the condition arising in the adult from thyroid atrophy, generally known as *myxœdema*, and the condition due to deficiency in early life, resulting in *cretinism*. Of this again, there are two varieties, namely the *sporadic cretinism* which may be met with in any locality and in which the thyroid is deficient or absent, and the *endemic cretinism* which is present in goitrous regions and is generally associated with enlargement of the gland.

Thyroid Deficiency

(1) **Myxœdema.** This term is usually applied to the condition resulting from thyroid deficiency in the adult, though the state of sporadic cretinism or infantile myxœdema due to congenital deficiency or absence, is essentially of the same nature. Myxœdema occurs chiefly in late adult life, though sometimes at a comparatively early period, and is commoner in women than in men. The skin becomes somewhat swollen and rather firm, smooth, dry and sometimes scaly. There is general atrophy of the hair follicles, and the hair of the head and other parts falls out to a varying degree, whilst there is marked diminution of the secretion of the sweat and sebaceous glands (Fig. 581). A certain degree of increase of the adipose tissue is often present. The circulation is imperfect, the heart's action and the

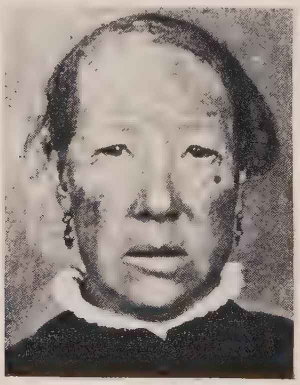

Fig. 581.[1]—Case of myxœdema showing the characteristic changes in the appearance.

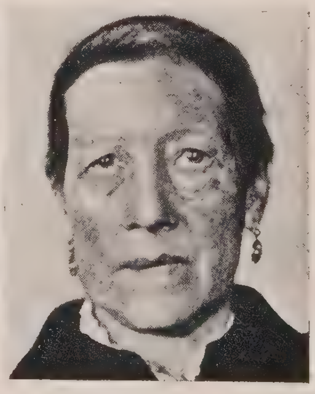

Fig. 582.—The same patient after 8 months' thyroid treatment.

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[1] I am indebted to the late Dr. John Thomson for the photographs from which Figs. 581, 582, 585, 586 are reproduced.

respirations are slowed and the patient suffers from cold; sometimes there is a distinct malar flush. The basal metabolism is distinctly lowered and the temperature tends to be subnormal. Also general hebetude, slowness of speech and sluggishness of movements are features of the affection, and these tend to become increasingly prominent. The sexual functions also are affected. In women, there is often amenorrhœa, whilst in men impotence tends to develop.

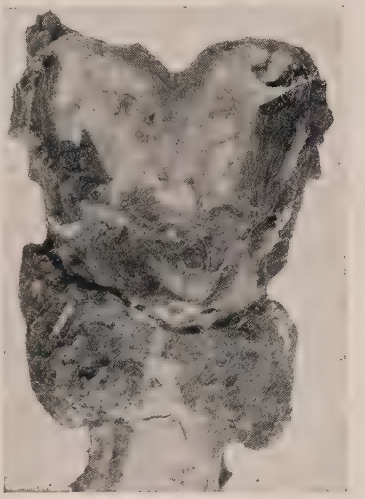
FIG. 583.—Thyroid in Myxœdema, showing irregular Fibrosis and Atrophy.

STRUCTURAL CHANGES. The changes in the thyroid may be said to be of the nature of a fibroid atrophy. The gland is diminished in size, sometimes reduced to a thin layer, has a tough consistence, and may be fairly smooth or somewhat nodular (Fig. 583). On microscopic examination, in advanced cases one may find that in parts the glandular tissue has disappeared and been replaced by fibrous tissue with extensive lymphocytic infiltration. In other parts all stages of atrophy and disappearance of the acini can be followed. The surviving acini are small and contain little colloid, some being reduced to small rings of cubical cells without colloid in the interior (Fig. 584). Small masses of epithelial cells and isolated cells may be scattered amongst the lymphocytic infiltration. The cause of these atrophic changes in the thyroid is still unknown; in a small proportion of cases they follow hyperplastic changes. The connective tissue of the skin is swollen, the collagen fibres are indistinct and there appears to be an excess of semi-fluid material, but the tissue is not really myxomatous in type. Excess of mucin has been found in some cases especially at an early stage, but it is not marked. The structures of the skin show atrophic changes. Similar change in the connective tissue may be

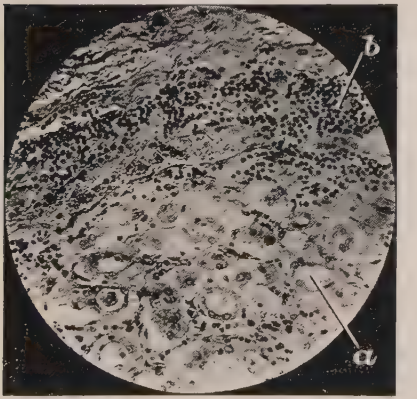

FIG. 584.—Section of Thyroid in Myxœdema, showing the atrophied remains of Acini (a) and Lymphocytic Infiltration (b). × 75.

present in other parts, for example in the interstitial tissue of the nerves, where it may be associated with a certain amount of atrophy of the nerve fibres.

Nature of the Disease. The various changes in structure and function met with in myxœdema are closely similar to those which result from removal of the thyroid gland for goitre—the condition known as *cachexia strumipriva*—and are undoubtedly due to deficiency of the thyroid secretion. This was conclusively shown by the therapeutic results obtained by thyroid treatment. Favourable effects were first obtained by transplanting portions of thyroid. It was then found that a similar result was produced by injection of the thyroid juice, and finally, that administration of the juice or of dried thyroid by the mouth was equally efficacious. By means of thyroid feeding, all the abnormalities described above may gradually disappear. Not only the functional disturbances but also the structural changes pass off; the hair becomes gradually restored, the aspect of the patient returns to normal, and sometimes also the mental activity. In fact, owing to the early recognition and treatment of the disease, myxœdema is not often seen nowadays in its fully developed form.

(2) **Sporadic Cretinism or Infantile Myxœdema.** This condition is due to congenital absence or hypoplasia of the thyroid tissue. It is met with from time to time in all localities, unlike endemic cretinism, and the causation of the defect is unknown. The thyroid lesion does not affect intra-uterine growth, the fœtus receiving a sufficient supply of thyroxin from the mother, and the effects of the lesion usually begin to appear about the second year of life. The growth of bone is markedly interfered with, and the cretin is stunted, or a dwarf; the defect in bone formation is a general one, including

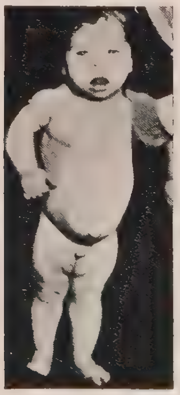

Fig. 585.—Child with sporadic cretinism, showing the characteristic features.

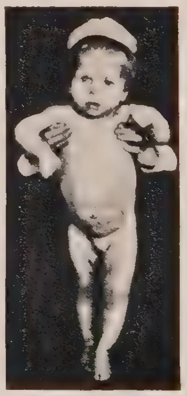

Fig. 586.—The same child after 2 months' thyroid treatment. The figure is on a somewhat smaller scale than Fig. 585.)

both endochondral and intra-membranous ossification, and thus the bones are smaller as well as shorter than normally. The cartilage at the epiphyseal lines persists long after the usual time of ossification ; there may be bony thickening in their neighbourhood and curving of the bones may occur. The base of the skull is shortened owing to diminished ossification in cartilage, the nose is depressed and the lips are thickened, so that a pig-like appearance results (Fig. 585). The skin is thickened, and in folds at places, and lipomatous tumours may be present about the shoulders and neck ; the hair is scanty and coarse. The abdomen is swollen and umbilical hernia is not uncommon. There is marked deficiency in intelligence, which may amount to idiocy ; the general aspect of a cretin, even of mature years, is childish.

In some cretins no trace of thyroid may be found, although in some such cases small nodules of atrophied thyroid tissue have been found near the foramen cæcum at the root of the tongue. In other cases the thyroid is small and shrunken, sometimes containing cysts, or only atrophied remains are present ; the occurrence of goitre is very rare (Fig. 587). The thymus is usually atrophied, but the parathyroids are not affected and occupy their usual position. The administration of thyroid extract may produce striking results in the condition of a cretin—considerable growth of bone, diminution of the abnormalities in appearance, and even improvement in the intelligence (Fig, 586). But such effects are obtained only when the treatment is carried out at an early stage ; beyond the period of normal growth there is comparatively little effect.

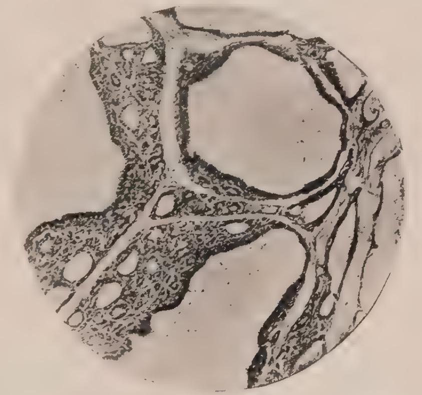

Fig. 587.—Nodular Goitre of unusual type, showing adenomatous areas and cysts with watery contents. A cretinoid condition was present. × 45.

(3) **Endemic Cretinism.** In goitrous districts cretins are not uncommon, and the condition is then known as *endemic cretinism.* Such cretins present the general features of the sporadic form just described, there being a similar defect in the growth of the bones, in the development of the genital glands, etc. All degrees of the condition are met with and in extreme cases the state is one of idiocy. An important point, however, is that deaf mutism is very often present as an additional condition. In the great majority of cases of endemic cretinism a goitre is present, although in some instances the thyroid is atrophic and fibrous. The goitre is nearly always of the

nodular form (p. 938), the gland being occupied by tumour-like nodules between which the rest of the parenchyma is compressed and represented by the atrophic remains of epithelial cells and colloid. Cretins of this type are nearly always the offspring of goitrous mothers and the goitre in the cretin is the result of thyroid deficiency during intra-uterine life. The goitre is deficient in activity for purposes of growth and thus the characteristic symptoms of cretinism appear. On the other hand the goitre of the mother may be sufficiently active to prevent symptoms from appearing in her. The cause of the deaf mutism is still obscure. It may be noted that thyroid treatment has been found less effective in endemic cretinism than in the sporadic form.

Hyperthyroidism

The term 'hyperthyroidism' is used as indicating increased formative and secretory activity of the gland, without implying that the secretion is of normal character. Recently, the term 'thyrotoxicosis' has been applied to the condition.

(1) **Exophthalmic Goitre.** This affection, which, as the name indicates, is associated with thyroid enlargement and exophthalmos, is characterised by a group of symptoms which, taken in their entirety, may be regarded as the effect of increased functional activity of the thyroid, or hyperthyroidism. The disease is much commoner in females than in males, and occurs most frequently in early adult life, though also at a later period. An important point is that the symptoms usually develop a comparatively short time after the thyroid enlargement. The patient suffers from tachycardia, twitchings, and tremblings, weakness, tendency to flushing of the skin and diffuse perspiration. In fact, the symptoms may be said to represent increased excitability and instability, especially of the sympathetic system. The basal metabolism is distinctly increased and may sometimes be 60 per cent. or even more above the normal, and there is not only increased respiratory change but increased excretion of nitrogen, which is often attended by loss of weight. The carbohydrate metabolism also is disturbed, there is a diminished tolerance of sugar and sometimes glycosuria is present.

In exophthalmic goitre the calcium metabolism also is affected. There is a withdrawal of calcium from the spongiosa of bones and increased excretion of it, but the blood calcium is not increased. The bones, with the exception of the cortex, become more porous and this is due to resorption by osteoclastic activity; there is no formation of osteoid tissue.

Structural Changes. The enlargement of the thyroid varies considerably in different cases. It is general in most cases (Fig. 588), though not infrequently one lobe is more affected than the other. Although enlargement is usually general it may be by no means uniform. Some parts may contain a considerable amount of colloid, others little ; there may also be nodularity of the surface. On section, the appearance of the parenchyma is altered, being less brown and less translucent than ordinarily, owing to diminution of colloid, and in many cases the gland substance is of a dull greyish-pink colour with lobular arrangement, the appearance somewhat resembling that of a salivary gland. The gland substance is moderately firm and somewhat succulent, though in advanced cases there may be a certain amount of fibrosis. Large veins are present on the surface and the superficial arteries may be enlarged, but the organ as a whole is not specially vascular.

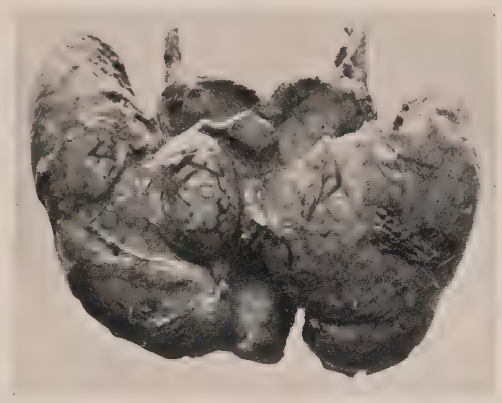

Fig. 588.—Thyroid in Exophthalmic Goitre.

On Microscopic Examination the changes found vary somewhat, according to the stage of the affection, but they may be said to represent chiefly hyperplasia of the epithelium and diminution of the colloid contents. The epithelial cells of the acini become increased in size and more columnar in type. Numerous small acini are formed, while in the larger ones papilliform ingrowths are often present, and the epithelium may be in more than one layer. While these changes are going on, the colloid becomes altered in quality and diminished in amount. At first it appears to be more watery and stains less deeply, and then gradually becomes absorbed as the growth of epithelium extends. Ultimately there may be little stainable material left, whilst the acini have become more numerous and smaller ; the increase in number, however, may be in part only apparent and due to the infolding of the walls of the acini. It is evident that the epithelial surface, as a whole, has become enormously increased (Fig. 589). These changes are usually interpreted as representing increased activity and increased formation of secre-

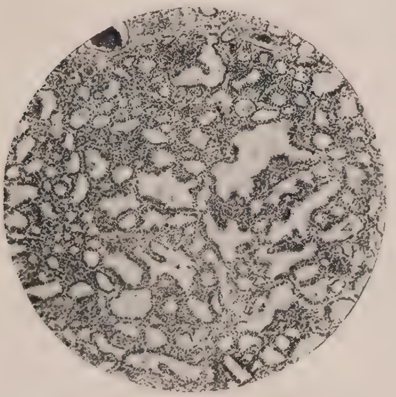

Fig. 589.—Thyroid Gland in Exophthalmic Goitre, showing epithelial Hyperplasia and disappearance of Colloid. × 75.

tion, which is, however, not retained but passed on to the blood stream. Not infrequently there is a considerable amount of lymphocytic infiltration, sometimes with the formation of small lymphoid follicles ; these changes are usually most marked in the superficial part of the gland. The alterations described are sometimes fairly uniform throughout the gland but that is by no means always the case. The gland often shows variations at different places ; in some parts active epithelial changes are present, in others there are quiescent acini which may contain a considerable amount of colloid. On microscopic examination of one portion of the gland one may fail to find changes which would indicate the presence of exophthalmic goitre. At a later period, when the acute symptoms are beginning to subside, colloid begins to reaccumulate and may be present in considerable amount. Thus the picture may be one of hyperplasia and subsequent involution irregularly distributed, and even fibrosis at places. In a number of cases the symptoms of myxœdema have supervened, but such an occurrence is exceptional.

Scott Williamson and Pearse, as a result of their investigations, draw a sharp distinction between the iodo-colloid of the normal gland and the ' secretion ' which replaces it in exophthalmic goitre, though they are related physiologically. They find that the secretion in exophthalmic goitre contains little or no iodine and has not the characteristic effect on the growth of the tadpole (p. 930).

The *thymus* shows distinct enlargement in fully three-quarters of the cases, this being due to general hyperplasia. There may also be some enlargement of the lymphatic glands and lymphoid follicles. In some cases hypoplasia of the chromaffin system has been found. Some observers consider that such changes are in proportion to the severity of the disease ; it is also held that death during or after operation may be due to this condition. A certain degree of hypertrophy of the heart occurs in most cases of exophthalmic goitre. Not infrequently there is diminution in the number of leucocytes per c.mm. in the blood, generally owing to a fall in the polymorpho-nuclears with relative lymphocytosis. Occasionally, however, there is an actual lymphocytosis, and this by some observers is believed to occur in the more severe cases.

The action of iodine is of interest. As is mentioned below (p. 940), the administration of iodine prevents the hyperplastic changes following removal of thyroid tissue, and it has a somewhat analogous effect in inducing retrogression of these changes in exophthalmic goitre. This has been demonstrated by Rienhoff, who removed portions of the diseased glands at different stages. He found that after treatment with iodine the epithelium becomes more cubical, whilst colloid accumulates in the acini. Later, accumulation in some of them becomes excessive and may lead to a certain amount of cyst formation. On the basis of these facts iodine treatment is now used as a pre-operative measure with beneficial results. It is clear that in some way the epithelial hyperplasia in exophthalmic goitre is bound up with iodine metabolism, but the relation is not fully understood. These changes may be followed by a certain improvement in the symptoms which, however, is not permanent.

Nature of the Disease. Though there are many points still obscure in connection with this disease, there seems little doubt that most of the symptoms are due to excessive production and absorption of secretion, in short, to hyperthyroidism. The contrast to myxœdema, which holds in nearly every respect, and the nature of the changes in the gland are in harmony with this view; also the fact that removal of the greater part of the gland brings about great amelioration of the symptoms, supports it. It has been suggested that the thyroid secretion is not only increased but of disordered nature; some recorded experiments support such a view, but the evidence is not complete. Regarding the cause of the change in the thyroid, however, nothing definite can be said. The fact that exophthalmic goitre has followed shock or fright suggests a nervous origin, the adrenals and the sympathetic system being possibly involved; and there is also the fact that the occurrence of the disease has relation to sexual events in the female. As already indicated, there is evidence that it may be preceded by changes in other endocrine glands, notably in the thymus. It would appear, in fact, that usually when there is a sudden onset of exophthalmic goitre there has been some pre-disposing constitutional abnormality.

(2) **Hyperthyroidism without Exophthalmos.** It has been shown in recent years, especially by American workers, that many of the symptoms of excessive formation of thyroid secretion may be present without exophthalmos. In cases of this kind there are increase of the basal metabolism, tachycardia, and also symptoms of hyperexcitability, in varying degree. Not infrequently the cardiovascular system is specially affected, and structural changes in the vessels and heart muscle may follow. Such symptoms are usually associated with the presence of nodular growths or adenomata in the thyroid, and, as a rule, these are of the parenchymatous type, being composed of small acini with little colloid, and masses of cells with imperfect development into acini; occasionally there is a more diffuse change. These adenomatous enlargements, which are evidently the results of repeated hyperplasia, commonly exist for a period of several years before evidence of hyperthyroidism occurs, the symptoms usually appearing gradually. The age incidence of the thyrotoxicosis is later than in the case of exophthalmic goitre, but the pathological state probably represents a milder degree of the same condition. Owing to the constitutional symptoms which are produced by them, the term *toxic adenomata* has been applied. In this variety of hyperthyroidism the results obtained by removal of part of the gland have been more successful than in exophthalmic goitre. Secondary operations at the Mayo Clinic, for instance, have been less fre-

quently called for. The condition is also known as 'secondary toxicosis.'

Goitre. The term 'goitre' or 'struma' is applied in a general way to any chronic enlargement of the thyroid of non-inflammatory nature. Tumour growth is often included in the term, thus 'malignant goitre' is spoken of; we shall, however, not consider at present the neoplastic enlargements. Varieties of goitre are usually distinguished as *colloid* and *parenchymatous*, there being in the former marked accumulation of colloid in the acini, and in the latter an increased formation of acini with little colloid. A distinction is drawn also between a *diffuse* form where the gland generally is involved, and a *nodular* form in which the increase occurs in scattered rounded areas of varying size; either of these types may be of the colloid or parenchymatous variety. Goitre is of common occurrence in certain districts, notably in the valleys of Switzerland, the Pyrenees and the Himalayas, in Derbyshire in this country, and in the region of the Great Lakes in America, and is thus spoken of as 'endemic goitre'; it may occur also sporadically in any locality.

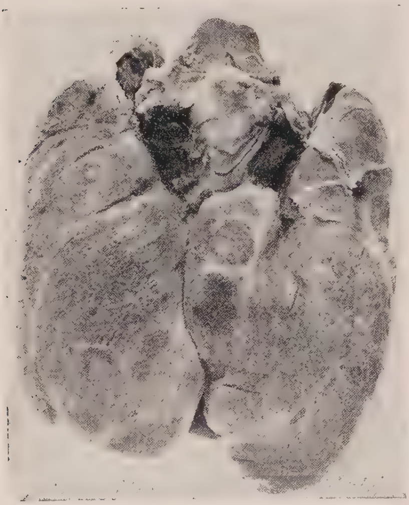
Fig. 590.—Diffuse Colloid Goitre with general enlargement of the Gland.

There are interesting variations in the distribution of the different types of goitre. In mountainous regions, e.g. the Alps, the common type is the parenchymatous, usually diffuse at first and becoming nodular later, and the affection appears early in life. Evidences of thyroid deficiency and cretinism are not uncommon, especially where the disease is very prevalent and of severe type. In America, on the other hand, goitre is in the majority of cases of the diffuse and nodular colloid type (Hellwig). It is much commoner in women than in men, and usually appears in connection with puberty or pregnancy; it may be regarded as a less severe type. The same seems to hold generally with regard to the disease in low-lying countries.

Structural Changes. In *diffuse* colloid goitre the whole gland may be affected (Fig. 590), or, on the other hand, one lobe may be chiefly involved; accessory thyroids also may undergo colloid enlargement. The gland substance is tense and firm, and on section presents a translucent brownish appearance due to the accumulation of colloid, which is usually pretty firm though sometimes semifluid.

There is a reticulated or honeycomb structure representing the stroma, and spaces of considerable size may be present. Dark red or brown areas due to hæmorrhage may be seen, and at places there may be fibrosis with not infrequently calcification of the stroma. On microscopic examination, it is found that the acini are of large size and distended with deeply staining colloid, whilst the epithelium may be somewhat flattened owing to the accumulation (Fig. 591). Larger spaces may be formed by the confluence of acini. In the parenchymatous type the tissue is less homogeneous and translucent in appearance, and there is an extensive new formation of acini which contain little or no colloid. There is evidence that a parenchymatous or hyperplastic stage precedes the colloid stage and it would appear that in the evolution of goitre these changes often occur in different parts of the gland at different times. In goitrous districts in Switzerland it has been found that the average weight of the thyroid at birth is fully double the normal, and occasionally a goitre of the parenchymatous type may be present, the so-called *congenital goitre*. In the *nodular* type of goitre a great variety of structure may be met with. There may be only one or two nodular masses, or, on the other hand, the gland may be studded with them, the parenchyma between becoming atrophied. Here also both parenchymatous and colloid types are met with, and all intermediate varieties. As a rule, the presence of goitre is not associated with distinct functional effects or constitutional symptoms, though recent observations show that minor evidences of disturbance are not so rare as was supposed. The enlarged gland may, however, bring about important results by pressure, especially on the trachea, which may become much narrowed, and thus even death by suffocation may follow. As has been mentioned above, in the goitre of mountainous regions the thyroid enlargement in children, usually of the nodular type, may be associated with a condition of cretinism, there being in such cases absence or deficiency of the thyroid secretion (p. 933). On the other hand, in America colloid goitre is not infrequently associated with some degree of thyrotoxicosis.

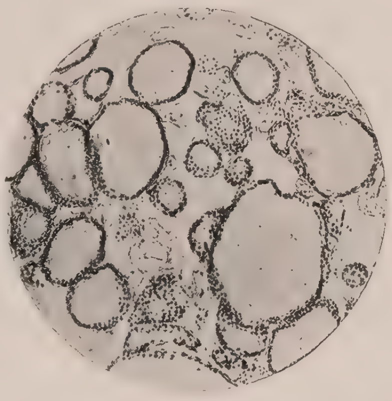

Fig. 591.—Colloid Goitre, showing accumulation of Colloid in Vesicles with cubical type of Epithelium. × 40.

Etiology. The causation of goitre cannot be said to be fully understood, but recent observations in America, especially, have proved that deficiency of iodine is the chief factor in the production of goitre in that country. The work of Marine and others shows definitely that such deficiency brings about a condition of hyperplasia of the thyroid, and that this may be followed by an accumulation of colloid. Excision of part of the thyroid in a normal animal leads to hyperplasia of the surviving part, but if iodine is administered at the same time such hyperplasia does not occur. Hyperplastic changes are thus stimulated or prevented according as there is defect or excess of iodine in the food ; accumulation of colloid may follow the hyperplasia if the iodine defect is not too great. These results have been practically applied on a large scale in the region of the Great Lakes, and it has been found that by the administration of small quantities of iodine to school children a remarkable diminution in the incidence of goitre has been effected. The preventive action of the results have not been so striking. In New Zealand, for example, the results have been on the whole disappointing. The epidemiology of goitre mainly depends upon the deficiency of iodine in the soil and drinking water. Thus in goitrous districts the disease affects also animals such as rats, dogs, sheep, etc., and this fact alone shows that there must be a widely acting cause. When the deficiency is great the affection appears at an early stage ; when it is moderate goitre is not only less common but also appears later, occurring especially in women when there is a drain on the iodine supply in such conditions as pregnancy and lactation. In the early stages especially, treatment by iodine is often of great benefit ; the thyroid enlargement is arrested and may undergo retrogression.

While it has been established that goitre is produced by iodine deficiency and can be prevented by administration of iodine, these facts do not explain its whole pathology. Goitre may be prevalent in places where there is no deficiency of iodine and it is possible that unsuitable or vitamin-deficient diet, or possibly infective conditions of the bowel, may play a part. Of this latter factor McCarrison has adduced strong evidence from observations in India. He has pointed out the striking variations in incidence of goitre in different districts of the same region, and considers that this is largely due to bacterial pollution of streams. A high calcium content of drinking water is believed by various observers to increase the incidence of goitre. The occurrence of sporadic goitre also requires explanation. It has been suggested that it may result from deficient absorption of iodine or from deviation in the body, but evidence is wanting. In view of what has been established, however, it must be admitted that iodine deficiency is the all-important causal factor in goitre.

Inflammatory Changes

The thyroid gland is comparatively rarely the seat of bacterial invasion with resulting inflammation. Acute thyroiditis is occasionally met with in acute specific fevers, influenza, rheumatism, typhoid, etc., and more frequently in women than in men. There are said to be epithelial proliferation and desquamative catarrh of the acini with increased fluidity of the colloid. Also a varying amount of interstitial infiltration by leucocytes occurs. Occasionally fibrosis may follow, and it is possible that fibrotic atrophy with myxœdema may sometimes be the result. Some observers consider that hyperthyroidism and even exophthalmic goitre may be started by such acute lesions. Sometimes infection with pyococci occurs and multiple minute abscesses are produced in the gland ; they are met with in pyæmic conditions, puerperal infection, etc. Occasionally an abscess of considerable size may arise in this way.

Tuberculosis of the thyroid is comparatively uncommon. Miliary tubercles may be present in cases of acute general tuberculosis, and occasionally chronic lesions are met with. The latter may be due to infection by the blood stream or to spread from adjacent lymphatic glands ; considerable enlargement of the thyroid with caseation has sometimes been observed, a condition of *tuberculous struma*. *Syphilitic lesions* have been described, but they are all very rare. They are of the usual types, gummata and diffuse fibrosis, and have been met with both in the congenital and acquired forms of the disease, more frequently in the former.

The two following conditions are usually described as examples of thyroiditis, but their true pathology is doubtful. They may, however, be conveniently considered here.

Riedel's Disease and Hashimoto's Disease. In 1896 Riedel described a type of thyroid enlargement or struma which was characterised by extreme hardness and smooth surface and by the extension of fibrotic changes to adjacent structures. Cases supposed to be of similar nature were reported by other writers but many of these showed a more cellular stroma in which the formation of lymph follicular tissue was a prominent feature. Hashimoto in 1912 described the features of several such cases, and considered that the condition was different from that described by Riedel ; he applied the name *struma lymphomatosa*. It has also been called ' lymphadenoid goitre ' (Pearse and Williamson). There is no doubt that the term Riedel's disease has been used in too comprehensive a way and that most cases correspond with Hashimoto's description. The following are the chief features of the two types of disease.

In Riedel's struma or thyroiditis, the characteristic features are the hardness of the gland, exceeding that of a scirrhous cancer, and the implication of adjacent structures in dense fibrous tissue. The latter makes the removal of the gland very difficult and an important point is that after removal the fibrosis continues to spread. The condition often gives rise to serious pressure effects. The enlargement, which is not so great as in the lymphomatous type, may affect the whole gland but not infrequently it affects mainly one lobe or may be partial. The surface is smooth. On microscopic examination the essential change is connective tissue overgrowth, varying from different degrees of cellularity to dense stroma formation. The acini undergo a progressive atrophic change and many disappear in considerable areas. Foreign body giant-cells may be present, apparently in relation to their atrophic remains. The term *struma fibrosa* might be a suitable name. A noteworthy feature is that there is little or no evidence of thyroid hypofunction and myxœdema does not supervene, unless after surgical removal.

In the Hashimoto type the enlargement is greater and of uniform nature ; and though the consistence of the gland is firm it is not of stony hardness. The capsule is thickened but there is no periglandular fibrosis with implication of adjacent structures. On microscopic examination there is found an extensive and often diffuse infiltraton of lymphocytes between the gland acini, and in these lymph follicles with germ centres are often a prominent feature. The acini are in varying states (Fig. 592). In many colloid is still present but in diminished amount, and it may show variations in staining. In others the epithelium may have a hypertrophic appearance or may be in various stages of atrophy, or again, may form syncytial masses. In advanced cases the acini may have disappeared in parts. At an early stage of the disease there may be some hyperfunction in the form of increased basal metabolism, but later some degree of hypofunction appears and this ultimately may be followed by myxœdema.

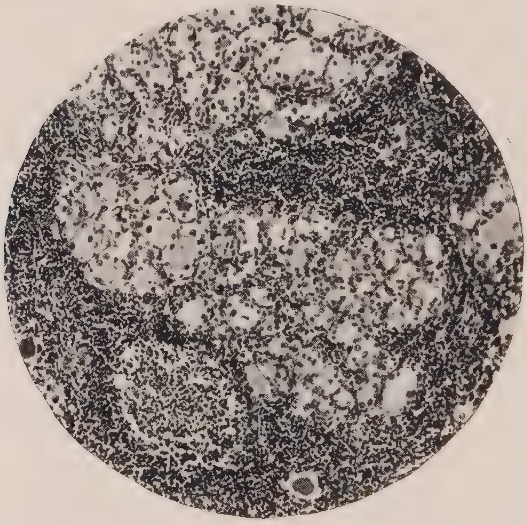

Fig. 592.—Thyroid in Struma Lymphomatosa (Hashimoto), showing extensive Infiltration of Lymphocytes and retrogressive changes in Acini.

Note germ centre in lower part of field. × 100.

As to the relation of the two affections, it has been considered by most writers, including myself, that they represented stages of the same affection. There are, however, weighty facts in support of the view that they are distinct as maintained by Joll. In addition to describing the differences mentioned above, he has pointed out that they differ also in their incidence. The Riedel type is met with at an earlier period of life than the Hashimoto type, and is commoner in males than females, whereas the latter type is commoner in the female sex. It seems to me until it has been definitely shown that the lymphomatous change is followed by dense fibrosis, it would be better to regard them as separate. It would appear that cases of the Riedel type are usually fibrous from the beginning. It may be added that the Hashimoto struma is eminently sensitive to radium and has been treated by it with success; further, unlike the Riedel struma, its surgical removal is not attended with difficulty.

Nothing is known with regard to the etiology of either condition. The dense fibrous tissue formation in Riedel's struma with marked implication of adjacent structures presents almost a unique pathological change, though Pick's disease presents similarity in some respects. We may call it a chronic fibrotic inflammation, though that is little informative. As to the Hashimoto or lymphadenoid type, in view of other conditions in which lymphocytic infiltration occurs in the thyroid it appears not unlikely that the state of the interstitial tissue represents a condition secondary to some abnormal or dyscrasic state of metabolism in the glandular tissue. As to the nature or causation of this, however, it is not possible to say anything.

Degenerative Changes

Apart from the gross lesions already described, degenerations are comparatively rare and of little importance. Evidences of damage produced by toxins are found in infections, as has already been described in connection with the inflammatory changes; and actual necrosis of the epithelium has been met with. Amyloid degeneration sometimes occurs as part of a general condition, and is usually slight in degree. Occasionally, however, it is well marked, and this has been found to be the case especially in thyroids already the seat of goitre or adenomatous swellings. Hyaline change, calcification, etc., are often present in the stroma of chronic goitres.

Tumours

Simple tumours such as fibromata and osteo-chondromata are occasionally met with, but are rare. Adenomata, on the other hand, are comparatively common. The occurrence of glandular nodules in goitres has already been mentioned, and closely similar masses are not seldom observed in otherwise normal thyroids. In fact, it is not possible to draw a line between circumscribed hyperplasiæ and true tumours. Adenomata are sometimes solitary, but are usually multiple, and they present various types of structure corresponding with stages in the development of the acini (Fig. 593). Some of them are composed of strands and cylinders of cells with imperfect formation of acini and little colloid; they are sometimes called 'fœtal adenomata,' but there does not seem to be sufficient evidence that they are always due to errors in development. In others, the acini are well formed but small and contain little colloid, whilst in others again, there may be considerable accumulation. Occasionally a papilliform type of growth is met with in adenomata, and sometimes cystic change occurs. As already mentioned, adenomata, especially of the more cellular type, are sometimes associated with symptoms of hyperthyroidism. Adenomatous nodules are not infrequently followed by malignant change in the later years of life. Adenoma of parathyroid origin is occasionally observed in the substance of the thyroid (p. 956). In connection with this subject it is to be borne in mind that the occurrence of aberrant portions of thyroid tissue is not uncommon. These may be in various positions in the neck, e.g. at the base of the tongue and also at a lower level, for example, behind the sternum; and they may become the seat of tumour growth or of goitrous enlargement.

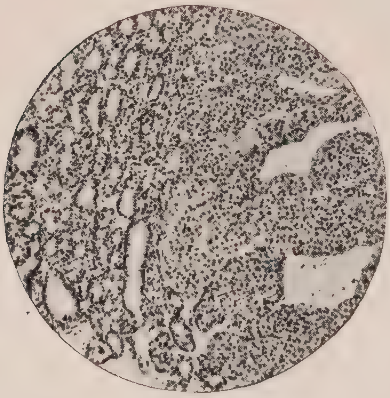

FIG. 593.—Adenoma of Thyroid, showing two types of growth—acinous type on left side of field and more solid type of growth on right. × 80.

Of the *malignant* growths, carcinoma is by far the commonest variety. The growth often remains circumscribed for a considerable time. It then infiltrates and breaks through the capsule of the gland and spreads to the surrounding tissues, often invading the wall of the trachea; metastases by the bloodstream may occur at an early stage. There is a clear relationship between the origin of carcinoma and some previously existing abnormality of the thyroid. In districts where goitre is endemic, notably in Switzerland, the incidence of cancer is much higher than in non-goitrous regions. Exophthalmic goitre, however, does not tend to be followed by malignant disease. This is apparently due to the comparatively rapid onset and the absence of long-continued previous structural changes which might act as precancerous. Apart from goitre carcinoma develops most frequently in connection with an adenoma, and in most cases the malignant growth has the structure of an adenocarcinoma, in which there may be distinct formation of colloid material by the cells; papillary form of growth is sometimes present. In cases of adenomata of the thyroid it is often very difficult to decide whether or not carcinomatous change has begun. In other forms, again, the growth is of a more irregular type, and all transitions to solid alveolar carcinoma occur. Secondary growths of both types of cancer occur not infrequently in the bones, and may be in large numbers. Here also formation of colloid may take place. The metastases, as a rule, give rise to destructive changes rather than sclerosis. Occasionally, squamous epithelioma may be met with in the thyroid, and it may possibly arise from the epithelium of the thyro-glossal duct. The combination of sarcomatous growth with carcinoma has been described in quite a number of cases, and we have seen an example where the apparently sarcomatous portion was very voluminous.

Sarcomata of various types—round-cell, spindle-cell and mixed-cell—are met with, but they are relatively rare.

Thyro-glossal Cysts. The middle lobe of the thyroid is formed by a down-growth of a tube of epithelium from the base of the tongue (foramen cæcum). The upper portion of this tube above the hyoid bone is lined by squamous epithelium. If this persists and if the buccal end is obstructed it may give rise to a 'lingual dermoid.' The lower part of the duct below the hyoid bone is lined by columnar ciliated epithelium. Thyro-glossal cysts may take origin from this part when it does not undergo involution. Such a cyst may rupture on the skin surface, forming a median cervical fistula. In the walls of these cysts portions of thyroid tissue are sometimes found.

THE PANCREAS

The lesions of the pancreas as a digestive gland have already been described (p. 639), and we have to consider here only its function as an organ with internal secretion. This function is concerned with carbohydrate metabolism and the hormone formed by the pancreas is essential for the utilisation of sugar ; when it is absent or markedly deficient, diabetes results. It is thus spoken of as an anti-diabetic hormone. There was up till recent times controversy as to the site of production of the internal secretion of the pancreas, but it was established by the work of Banting and Best that it is formed in the islands of Langerhans ; it is accordingly now known as *insulin*. We shall in the first place give an account of the main features of diabetes and then discuss its relationship to the pancreas ; we shall afterwards refer to other conditions where glycosuria is present.

Diabetes. In diabetes there is a failure in varying degree to store and metabolise glucose, with a resulting excess of that substance in the blood and consequent glycosuria. The failure to store sugar in diabetes is shown by the diminution of the amount of glycogen in the liver and muscles and also by the phenomena which occur when glucose is given to a diabetic patient. The inability to metabolise sugar is shown by its increase in the blood and its discharge from the body and by metabolic changes resulting from its loss, there being in severer cases an increased metabolism of proteins to supply energy. Normally, the blood contains glucose in the proportion of about 0·1 per cent., this figure rising somewhat after ingestion of carbohydrates. When the amount rises to about 0·18 per cent. the glucose is excreted as such by the kidneys, or, to speak more correctly, is excreted in such an amount as to be detectable by Fehling's solution or other chemical test. In human diabetes there is always hyperglycæmia, the glucose sometimes reaching 0·4 per cent., and the glycosuria is merely a necessary secondary result. In the condition of phloridzin diabetes, produced experimentally by administration of the glucoside phloridzin, on the other hand, the glycosuria is due to a lowering of the kidney threshold for sugar, and thus the amount of sugar in the blood falls below normal (p. 952).

In diabetes there is much thirst and the patient drinks an excessive amount of fluid. This is due to the polyuria, which in its turn results from the interference with the re-absorption of water in the renal tubules by the glucose present. The urine is pale and, owing to the presence of the glucose, of high specific gravity. In severe cases of diabetes, owing to the failure to utilise glucose, proteins and fats are metabolised in increased amount and the glucose derived from the former is excreted in the urine. Thus, when carbohydrates are excluded from the diet there may be still in the urine a considerable amount of sugar derived from proteins, and the relationship between the amounts of glucose and of nitrogen excreted may correspond to that in pure protein metabolism. Further, as energy has to be derived chiefly from the oxidation of proteins and fats, there is a marked fall in the respiratory quotient ; that is, there is a fall in the amount of oxygen discharged in the form of carbon dioxide relative to the amount of oxygen absorbed by the lungs. The respiratory quotient (CO_2/O_2) for pure carbohydrate metabolism is, of course, unity, but in diabetes it may fall to 0·8 or even a lower figure. Owing to the increased metabolism of proteins and fat for the supply of energy, and also as a result of the fact that fat is no longer formed from carbohydrates, marked emaciation occurs. The abnormal metabolism necessarily leads also to muscular weakness.

An important phenomenon in diabetes is the appearance of *acetone bodies* in the urine (*ketonuria*), these comprising acetone, diacetic acid, and β-oxybutyric acid. The last, which is the least highly oxidised member of the series, is the substance which becomes most abundant in severe cases of the disease, and hence the amount in which it occurs is of special importance. Thus the amount of oxybutyric acid in the urine may reach 50 grammes per day or more, whilst the amount of diacetic acid and acetone together rarely exceeds 5 grammes. The utilisation of carbohydrates by the tissues is essential to the proper oxidation of fats, and in the absence of the former, the acetone bodies are formed as the result of the imperfect oxidation of the higher fatty acids, and appear in the urine. This occurs, for example, in starvation, or when carbohydrates are excluded from the food ; whilst in diabetes inability of the tissues to utilise glucose leads to the same result. The amount of the acetone bodies in the urine thus supplies an index of the degree of failure in this power, and an abundance is of grave omen.

In cases of diabetes, there is often an increase of fat and lipoidal substances in the blood. Occasionally this is so marked that the blood serum has a turbid appearance, and when the blood is allowed to stand, a white film composed of fatty globules gathers on the surface. The cholesterol content of the blood is usually increased, and not infrequently there is a deposit of cholesterol esters in the skin, resulting in yellow patches of xanthelasma (p. 149). Accumulation of lipoids may occur in the reticular and endothelial cells of the spleen, and occasionally this is so great as to lead to marked enlargement of the organ. A pronounced fatty change in the kidneys is fairly common, and this is frequently accompanied by accumulation of glycogen, especially in Henle's tubules (p. 176). Both of these changes probably represent a reabsorption from the glomerular filtrate.

The addition to the blood of diacetic and oxybutyric acids produces a state of *acidosis*. The term does not mean that there is a change in the hydrogen-ion concentration of the blood, but simply that acids are constantly being added to it, and alkalies constantly required for their neutralisation. This is at first effected by the fixed alkalies, but in order that these may not be completely used up, there is an increased diversion of ammonia from the normal formation of urea from protein, and the ammonia is used for neutralising the acids. Along with the acidosis in diabetes, there is thus an increased amount of ammonia nitrogen in the urine. As has been already indicated, there are different degrees in the disturbance of carbohydrate metabolism, and many diabetics can utilise sugar to a varying extent. In such cases, if the patients are put on a strict diabetic diet, i.e. a diet as far as possible free from carbohydrates, the oxidation of fats is still further interfered with, acidosis is increased and harm results. The practical importance of adjusting the diet to the power of utilising carbohydrates is thus apparent.

In quite a large number of cases of diabetes death occurs from *coma*, which is in some way the result of the acidosis. The onset is usually indicated by air hunger and deep respiration. The venous blood is redder than the normal, and contains a diminished amount of carbon dioxide. These changes are due to the fact that whilst the sodium carbonate is spared to a considerable extent by the deviation of ammonia, as explained above, it ultimately becomes diminished in amount because the sodium is used for neutralising the acids in the blood, and thus the convection of carbonic acid as sodium bicarbonate from the tissues to the lungs is interfered with. The respiratory centre and tissues generally suffer from a degree of asphyxia. Similar phenomena occur when acids are introduced into the circulation experimentally. This is probably not the whole explanation of diabetic coma, as while the injection of alkalies may relieve the symptoms, any relief is only temporary and the fatal result is not averted. It is thus possible that the condition of acidosis leads to actual damage to the nerve cells.

Another important change in diabetes is a greatly increased susceptibility to bacterial infections. Boils and carbuncles are of frequent occurrence and occasionally there follows a blood infection with secondary abscesses in internal organs. Diabetics not infrequently become infected with tubercle, especially of the lungs, and the disease is apt to run a rapid course. Again, inflammatory conditions may assume a specially severe type ; for example, pneumonia may be followed by gangrene of the lung. Peripheral neuritis is another complication met with and trophic disturbances, such as perforating ulcer of the foot, may result. Marked atheroma, apparently related to high cholesterol content of the blood, is often present and arterial thrombosis is apt to result. Thus gangrene of part of a limb is one of the recognised complications of diabetes (p. 136) ; coronary artery thrombosis is another.

Estimation of Blood Sugar.[1] The introduction of a clinical method for estimating the amount of sugar in the blood has been the means of showing the deficiency or failure in the power to assimilate or store sugar ; it has also supplied a valuable method of diagnosis in doubtful cases and of regulating treatment. When an amount of glucose, say 50 grammes, is given to a normal person, four or five hours after a meal, there soon occurs a distinct rise of the blood sugar, the maximum of about 0·15 per cent. being reached in half an hour or shortly thereafter. A comparatively rapid fall then occurs and the blood sugar reaches a normal level again in about an hour, or at any rate within an hour and a half. The rapid fall is apparently the result of the storage mechanism in the liver and probably also in the muscles coming into active operation, as, during the time of the fall, sugar is still being absorbed from the intestine. On the other hand, if the blood sugar of a diabetic patient be brought down to the lowest limit and 50 grammes of glucose be administered, the curve of the blood sugar is of quite a different character. It rises rapidly as before (there is no interference with absorption of sugar from the bowel in diabetes), and continues to do so for three or four hours, though the curve becomes less steep, and then there is a gradual fall which may go on for some hours. This shows that there is a deficiency in the normal mechanism of storage of sugar, which deficiency is one of the chief characteristics of diabetes. When the blood sugar rises above 0·18 per cent. or thereabout, glycosuria occurs, but in some cases of mild diabetes the blood sugar may rise to even a higher level without sugar appearing in the urine. The clinical estimation of the blood sugar is of great service in cases of slight or transient glycosuria, and it may be said that whenever the normal rise is followed by the normal fall, there is no fault in the storage mechanism and no diabetes. In some such cases, the glycosuria is simply due to the kidney threshold value being lower than normal, e.g. about 0·13 per cent., so that when glucose or much carbohydrate is administered and the blood sugar rises above this level, glucose is excreted by the kidneys. Such a condition is usually known as *renal glycosuria.* Patients with this abnormal threshold value may have a quite normal storage capacity, and little harm is done by the small loss of sugar due to what may be called a simple overflow. On the other hand, in the experimentally produced phloridzin diabetes, owing to the action of the drug on the kidneys, glycosuria occurs with a *normal* amount of blood sugar and continues till the amount may fall even below 0·1 per cent. ; the sugar thus drains away. If this form of glycosuria be produced in a starving animal, the available carbohydrate soon becomes used up and then there is an increased metabolism of protein for the supply of energy as in ordinary diabetes, while sugar formed from protein appears in the urine.

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[1] For details, see *Modern Methods in the Diagnosis and Treatment of Glycosuria and Diabetes*, by H. MacLean, M.D. London, 1922.

Relation of Diabetes to the Pancreas. It was shown in 1890 by v. Mering and Minkowski that the experimental removal of the pancreas in dogs produces a rapidly fatal form of diabetes. In the disturbances which result from the removal all the essential phenomena of the disease in its grave form, as above described, are present —hyperglycæmia and glycosuria, disturbed metabolism, wasting, acidosis, excretion of acetone bodies in the urine, etc. ; death, usually preceded by coma, occurs within three or four weeks. It was found also that the symptoms of disease do not develop when about a fifth of the gland was left in the body. That the diabetes is not due to loss of the pancreatic juice supplied to the intestine is shown by the fact that, when the duct is brought to the skin surface so that the juice is discharged externally through the fistula, diabetes does not follow. It thus became clear that the diabetes is the result of the loss of an internal secretion or hormone supplied by the pancreas.

It has been recognised for some time that complete obstruction of the pancreatic duct leads to atrophy and secondary fibrosis of the acini of the pancreas, and that ultimately the glandular tissue may largely disappear and be replaced by fibrous and adipose tissue ; on the other hand, the islands of Langerhans persist practically unchanged (Fig. 594). MacCallum excised half of a pancreas and by ligaturing the duct produced in the other half the atrophic changes described. No diabetes resulted, but when the atrophied pancreatic tissue containing the islands was removed, symptoms of grave diabetes developed. It was by taking advantage of the fact that the islands persist after ligature of the duct, that Banting was led to the discovery of insulin as the active agent concerned in diabetes. In collaboration with Best he tested the action of an extract prepared from a pancreas degenerated in this way, and found that the extract had a marked effect in diminishing glycæmia and the glycosuria in depancreatised dogs. The active principle concerned has since been known as *insulin.*

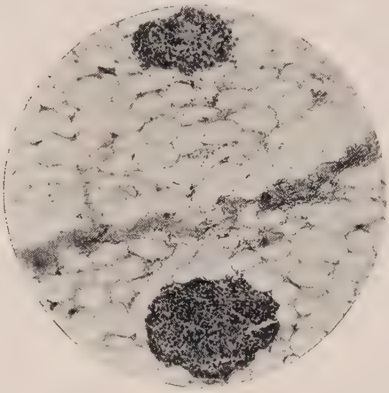

FIG. 594.—Fat Atrophy of Pancreas resulting from obstruction of the Duct.

The pancreatic tissue has been replaced by fat whilst the islands of Langerhans are well preserved—two are seen. (J. S. D.) × 45.

While lesions of the pancreas in diabetes in the human subject are commonly met with, the information supplied by pathological anatomy has been of an unsatisfactory kind. There may be said to be no one characteristic lesion associated with the disease. The changes met with have been of various kinds ; namely, simple atrophy, fibrosis with atrophy or 'granular atrophy,' chronic interstitial pancreatitis attended sometimes by enlargement, and occasionally carcinoma or calculus ; in some instances the symptoms of the disease have appeared after acute lesions. In such conditions the islands are frequently diminished in number or may be almost absent, but sometimes no lesion can be found. Opie was the first to describe hyaline change in the islands as sometimes occurring apart from other lesions ; the cells of the islands become gradually transformed into bands of refractile hyaline material, which may occupy a large proportion of the islands (Fig. 595). We have met with this lesion, but in only a relatively small proportion of cases of diabetes ; it is by no means a constant one. In other cases the islands are involved in fibrosis, and no doubt, as Opie has pointed out, the interacinous or intralobular form of pancreatitis is of special importance in bringing about this result. An important fact, however, is that in a considerable proportion of cases of diabetes a swelling or hydropic degeneration of cells of the islands has been described by Weichelsbaum and by Allen. Homanns observed similar changes to occur on the onset of diabetic symptoms in

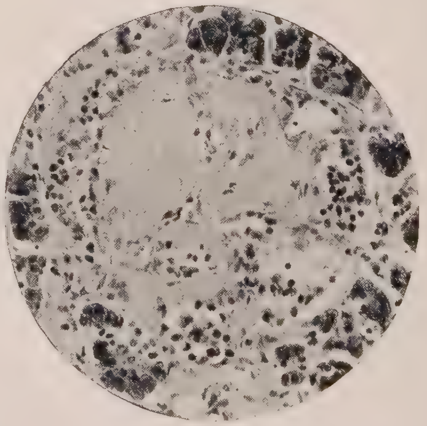

FIG. 595.—Island of Langerhans showing Hyaline Degeneration in a case of Diabetes. (Dr. John Cowan.) × 250.

animals from which the pancreas had been partially removed, and considered that they represented hyperactivity of the surviving cells. The cells, which showed the change, were the B cells. It has been established, notably by the observations of Lane and Bensley, that the islets of Langerhans are composed of cells of two types—A and B cells—which contain granules differing chemically and in their staining reactions. The granules of the B cells correspond in their solubility with insulin, and there is evidence that diabetes may depend on lesions of these cells. Increased functional activity of the islands, brought about by resection of pancreatic tissue, is followed in healthy animals by disappearance of the B granules; the cells become hydropic or vacuolated in appearance. It has also been found that administration of insulin restores the granules. These results are significant, but the primary cause of these lesions in the islets, when present in human diabetes, is not known. One may add that the methods of demonstrating the granules of the islet cells can be satisfactorily applied only to tissue fixed within a very short time after death. It will be seen from this account that knowledge as to the structural changes underlying diabetes is still unsatisfactory. At present no other lesion than one of the pancreas is known to produce a grave form of diabetes, though glycosuria may occur as a result of changes in other endocrine glands.

The administration of insulin to a diabetic patient is ordinarily followed by the disappearance of all the important features of the disease. The blood sugar falls, glycosuria and ketonuria disappear, the storage of glycogen in the liver and muscles again occurs and the normal metabolism of fats is regained. There is also a rise in the respiratory of quotient owing to the restored oxidation of carbohydrates. It may be said that in the normal animal the injection of insulin causes increased carbohydrate metabolism with hypoglycæmia, and the deposits of glycogen in the liver and tissues become diminished owing to the drain. This increased metabolism under the influence of insulin occurs in the tissues, as insulin does not cause directly increased glycolysis in the blood. A point of importance is that whenever the blood sugar falls below a certain level, there develop nervous symptoms, ultimately ending in convulsions, coma and respiratory failure. This is the case in the diabetic patient when insulin is given in excess, and also in the normal animal. Mann and Magath showed that acute symptoms follow removal of the liver and are due to hypoglycæmia. The symptoms are promptly relieved by administration of glucose and, by taking advantage of this fact, they were able to prolong the lives of dogs after the operation.

In the case of diabetes we have an excellent example of disturbance of the balanced action of two endocrine glands. In one sense the diabetes is the result of insulin deficiency, but in another sense it is due to the unopposed action of the pituitary. This is well shown by the fact that if in a depancreatised dog with diabetes the pituitary be excised, the symptoms of the disease are largely removed (Houssay). The power to store glycogen was restored and the hyperglycæmia and ketosis disappeared.

The opposite condition to insulin deficiency is exemplified by the increased production of insulin and the resulting hypoglycæmia which has been observed in some cases of tumours of the islands of Langerhans (p. 645).

Other Forms of Glycosuria. As has already been explained, excretion of glucose in the urine occurs when the amount in the blood rises above a certain level, that is, is the result of hyperglycæmia. The latter may be produced by excessive formation of glucose from glycogen in the liver and in the muscles, and may be brought about either through the nervous system or by means of the secretion of the endocrine glands ; and both of these factors may be involved. For example, increased formation of glucose and hyperglycæmia may be produced by stimulation of the sympathetic fibres going to the liver, and adrenine apparently acts in this indirect way. The best known example of glycosuria resulting from a nervous lesion is the glycosuria due to puncture of the floor of the fourth ventricle, discovered by Claude Bernard. This is the result of increased formation of glucose by the liver with consequent hyperglycæmia, and it does not occur when the store of glycogen in the liver is exhausted. The action on the liver takes place through the sympathetic fibres. It has been stated by some that this form of glycosuria is produced through the medium of adrenine, but Stewart and Rogoff have shown that the puncture or ‘ piqûre ’ glycosuria occurs when action of adrenine is artificially excluded, just as it does in normal animals. Glycosuria met with sometimes as the result of various lesions in the brain is apparently of the same nature. Examples of glycosuria due to excessive endocrine secretion are met with in exophthalmic goitre and occasionally also in acromegaly, and have already been referred to. The glycosuria which may result from narcosis, morphia, nitrites, etc., is apparently of nervous origin, and it has been shown, at least in the case of ether glycosuria, that adrenine is not concerned. In all these forms of glycosuria the increase of glucose is prevented or removed by the administration of insulin. In contrast to these examples glycosuria in the human subject may be due not to hyperglycæmia, but simply to a lowering of the threshold value for sugar so that it escapes more readily by the kidneys—renal glycosuria (p. 949). The extreme example of this is the glycosuria produced by phloridzin, as explained above ; in this instance the glycosuria leads to hypoglycæmia and great loss of carbohydrates. It is evident from what has been said that the term ‘ alimentary ’ glycosuria has no definite significance.

THE PARATHYROIDS

Experimental. It was first established by the work of Gley and of Vassale and Generali that the parathyroids are essential to life, and that their removal is followed by a group of relatively acute symptoms constituting a form of tetany—*tetania parathyroideopriva.* These symptoms vary somewhat in different animals, but the chief are general depression, fibrillar twitchings and jerking movements, spasms especially of extensor muscles, sometimes disturbance of the balance of the body, convulsions and emaciation ; a fatal result not infrequently follows within a few days. The nervous phenomena depend essentially on changes in the central nervous system, and there is hyperexcitability, especially of the lower motor neurons. There is also increased electrical excitability of the motor nerves as tested by the galvanic current, and this is resident mainly in the neuro-muscular junctions. It was shown by MacCallum and his co-workers that after parathyroidectomy there is a marked fall in the amount of calcium in the blood, that this produces an increased excitability of the nerves, and that the administration of calcium relieves the nervous symptoms.

In experiments where the parathyroids are partially removed, *latent tetany* may result, a condition where objective symptoms may be absent, but where there is the characteristic increased excitability of the nerves. It was found by Erdheim that in chronic tetany in rats, caused by partial parathyroidectomy, there was a deficient formation of enamel and dentine in the incisor teeth, so that they were apt to become broken across. Ossification also was interfered with and osteoid tissue was laid down, and fractures healed imperfectly in such animals with the formation of soft callus. These changes are apparently the direct result of the calcium deficiency in the blood, which results from parathyroidectomy.

After tetany and hypocalcæmia had been proved to result from parathyroid deficiency, attempts were made to prepare an extract from the parathyroid which would admit of substitution therapy. This result was obtained by Collip who showed that extracts prepared by weak hydrolysis of ox parathyroids contain the active principle or hormone generally now known as *parathormone.* The efficiency of the extract was shown by its removing tetany and hypocalcæmia after parathyroidectomy. At the same time a fall in the inorganic phosphorus of the blood occurs and also an increased excretion of both phosphorus and calcium in the urine. These and other facts show that the parathyroids have an intimate relation to phosphorus as well as to calcium metabolism ; in fact it is supposed by some that the action of parathormone is primarily on the phosphorus. Corresponding results were obtained in normal individuals, the blood calcium being raised by the administration of parathormone. When given in excessive doses to dogs it causes toxic symptoms, vomiting and diarrhœa, which may be followed by a fatal result. The hormone acts on calcium essentially as a mobiliser, removing it from the bones. When administered to animals for some time in fairly large doses the hypercalcæmia is followed by metastatic calcification in the arteries, kidneys, stomach, etc., very much in the same way as has been described in the case of vitamin D (p. 828). Calculi of calcium phosphate may form in the bladder. The mode of production of the hypercalcæmia is, however, quite different in the two cases. The occurrence of the essential changes of osteitis fibrosa has been found by Jaffe and Bodansky to follow the injections of parathormone in young dogs and guinea-pigs. Other observers have obtained negative results in this respect.

Tetany in the Human Subject. Tetany was of course recognised as a distinct affection for a long time before anything had been established as to the functions of the parathyroids, and was known to occur in a number of different conditions. It had been found to follow thyroidectomy for goitre in some cases, and this form, known as 'post-operative tetany,' can be definitely ascribed to removal of, or damage to, the parathyroids. Tetany is a not uncommon condition in children, and the presence of rickets is associated with it in a large proportion of cases. In these the calcium content of the blood has been found to be reduced, sometimes to half the normal. Tetany is met with also during pregnancy and lactation, and is apparently due to a drain of calcium. There is, too, a well-recognised variety, known as 'gastric tetany,' which occurs in cases of dilatation of the stomach with fermentative changes in its contents, especially, it is said, when the dilatation is due to obstruction at the pylorus. Gastric tetany is related to, and probably depends on, a state of alkalosis induced by the vomiting and consequent loss of hydrochloric acid from the stomach. The alkalosis (which, however, may be absent in other forms of tetany) is believed to lead to a fall in the calcium content of the blood. Tetany develops sometimes in the course of infective diseases, e.g. influenza, rheumatism, etc.; further, its occurrence is related to certain trades, especially those of sedentary nature—the so-called 'occupation tetany.' In the various forms the symptoms vary considerably but are mainly spasms of the muscles, which are usually paroxysmal but sometimes of a persistent character; fibrillary contractions also occur in the muscles. The muscles of the limbs are specially affected, but others may be involved, for example, those of the larynx and pharynx.

Along with these active manifestations, there is found an increased excitability of the nerves to electrical and mechanical stimulation, of nature similar to that met with after parathyroidectomy, and here also the hyperexcitability may exist without the actual presence of spasms, thus constituting a latent form of tetany. These facts with regard to tetany have been given here as the symptoms are of the same nature as those following parathyroidectomy, but tetany does not ordinarily depend on a lesion of the parathyroids. The essential factor is a disturbance of the calcium-phosphorus metabolism, hypocalcæmia playing the chief part in the production of symptoms; alkalosis also may be concerned. The disturbance may be produced in various ways. The tetany of rickets, for example, is due to diminished absorption of calcium owing to the deficiency of vitamin D and can be cured by administration of the vitamin or by irradiation. It is generally regarded that enlargement of the parathyroids which may be met with in rickets is secondary to the disturbance of calcium metabolism, and probably represents a work hypertrophy. Hæmorrhage into the parathyroids has been found sometimes to occur at the time of birth, and it is possible that a certain amount of deficiency may be brought about in this way. The possibility of functional disturbance of the parathyroids must also be borne in mind. On the whole, however, there is not satisfactory evidence that tetany, as met with either in children or in adults, is often due to a primary hypofunction of the parathyroids.

Parathyroid Hyperfunction. This is seen in a chronic form in cases of generalised osteitis fibrosa due to a parathyroid adenoma. The osseous changes in this disease have already been described, but it may be recalled that they are essentially the result of withdrawal of calcium from the spongiose of bones under the influence of excess of parathormone. The hypercalcæmia, increased excretion of calcium and phosphorus, and the occasional metastatic calcification are the results of this. The number of cases in which parathyroid adenoma has been present is now large, and in a considerable proportion removal of the tumour has been followed by striking results. Usually there is a single tumour of somewhat oval form, often of somewhat yellowish tint, and varying in size; it may reach more than 2 in. in length but is usually smaller. It is, however, noteworthy that severity of the symptoms has no relation to the size of the tumour. Sometimes there is more than one growth. The removal of such growths has demonstrated clearly that the metabolic disturbance is the result of parathyroid hyperfunction. The amount of calcium in the blood falls at once and the excretion of calcium and phosphorus in the urine becomes diminished. While there may be a restoration of calcium metabolism to a normal state, this, however, is not always the case. Sometimes the blood calcium is little diminished, which may be due to the presence of an adenoma in another parathyroid. On the other hand, the removal of an adenoma may be followed by a fall of the blood calcium to an abnormal level and sometimes tetany appears. The tetany may be removed by means of parathormone but occasionally it is intractable and may lead to death by exhaustion. The occurrence of such an untoward result suggests that the remaining parathyroids are not functioning fully, as removal of a single parathyroid does not usually lead to serious effects. The matter, however, requires elucidation. The tetany may sometimes be cured by administration of hydrochloric acid along with increased intake of all mineral elements (Telfer). In cases of parathyroid adenoma where excision of the growth has a favourable result as regards metabolism, retrogression of the changes in bones follows but it is of slow nature.

Tumours. The commonest form of tumour is the adenoma, and in a considerable proportion of cases this has been associated with hyperfunction and disturbance of calcium metabolism ; statistics with regard to this association are still wanting. The general characters of the growth have already been given. Microscopic examination shows that the cells constituting the growth correspond with those of the normal gland—chief or principal cells, different forms of oxyphil cells (Fig. 596). The proportions in which the different types occur vary. The cells are often larger than the normal cells and their nuclei may show hypertrophic changes and may be multiple. They often contain a considerable quantity of glycogen. Cells of columnar form may occur and a papillary type of growth may be present in an adenoma. It is to be noted that an adenoma may be incorporated in the substance of the thyroid. Carcinoma may arise in a parathyroid but is very rare.

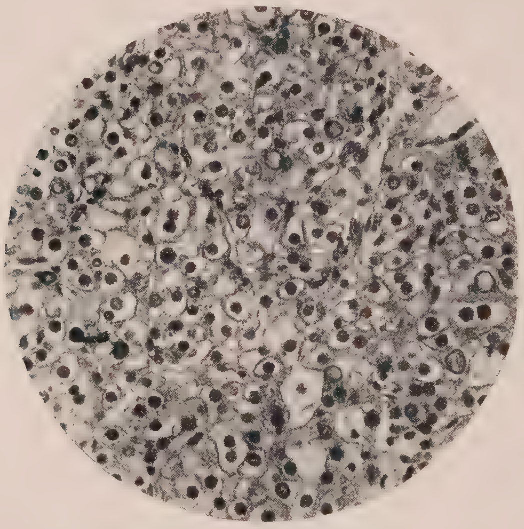

Fig. 596.—Section of parathyroid from a case of generalised osteitis fibrosa, showing the characters of the cells. × 200.

THE ADRENALS

Introductory. In connection with the pathology of the adrenals the double constitution of the glands is of great importance, and in this respect they present an analogy to the pituitary. The essentially different structure and developmental origin of cortex and medulla are, of course, generally recognised ; they are in all probability functionally interrelated, but to what extent is still obscure. We shall first of all consider some facts with regard to the cortex, which is of mesodermic origin.

It may be regarded as established that removal of the whole of both adrenals is followed by death usually within a comparatively short time. The time of survival varies in different animals but is ordinarily a matter of a few days. In rats the period is not infrequently lengthened and this is probably due to the presence of accessory cortical tissue. After double adrenalectomy the animal shows little ill effects for some days but about a day or two before death serious symptoms appear. It becomes dull and stupid and shows weakness and uncertainty in movements. Apathy and asthenia and cardiac weakness become progressive until the time of death, which is preceded by a marked fall of temperature. There is also a decided fall in the sodium content of the blood and a rise in potassium and also magnesium. All these symptoms have an important bearing on human pathology and have been shown to depend on loss of the cortical substance. Various cortical extracts have been prepared and by means of them the life of animals can be indefinitely prolonged. The effects of such extracts are truly dramatic. An adrenalectomised animal in a state of collapse and with a temperature more than five degrees below normal may be brought to a practically normal state within twenty-four hours. Active cortical extracts have a certain effect when given by the mouth but are much more effective when given by parenteral injection. The effects in the human subject are considered below. The adrenal cortex has also an intimate relation to the gonads, producing increased activity, but this must be a subsidiary matter so far as the acute effects of complete deficiency are concerned. A very interesting fact is that a tumour of its cells has a striking result in affecting the secondary sexual characters.

The adrenal medulla is of neuro-ectodermic origin and contains two main types of cells. The mother cells are the sympathogonia and from these are derived, (*a*) the ganglionic cells through the sympathoblasts and (*b*) the phæochromocytes or chromaffin cells through the phæochromoblasts. As will be described below, from both classes of cells interesting tumours arise.

The chromaffin cells which have the property of reducing chrome salts are the source of adrenaline, now usually known as adrenine or epinephrine. The pharmacological action of this substance has been extensively studied but it is necessary to refer to only two subjects, namely, its relation to blood pressure on the one hand, and its relation to sugar metabolism on the other. It has been established that there is increased discharge of adrenine into the blood as an emergency action in conditions of emotion, fright, exposure to cold, etc., but it is not clear that it is concerned in any material degree in maintaining normal vascular tonus. A view formerly held was that adrenine played an important part in pathological conditions of high blood pressure, but this has not been substantiated. The only known condition of disease in which its production is definitely increased is the adenoma of the chromaffin tissue (p. 965). The other important effect of adrenine is the production of increased glycogenolysis both in the liver and in the muscles and thus to increase of the blood sugar. This effect corresponds with what may be induced by stimulation of nerves of the sympathetic system, hence adrenine and other substances acting in a similar way have been termed ‘sympathominetic.’ Adrenine may thus be concerned in various types of glycosuria described above, its output being stimulated by the secretions of other endocrine glands or through the nervous system.

So far as human disease is concerned the disturbances of endocrine function to be considered are :

A. Hypofunction, (1) Chronic—Addison's disease ; (2) Acute—Adrenal apoplexy.

B. Hyperfunction, (1) Cortical ; (2) Medullary. This is known definitely to occur only in cases of adenomatous growths.

A. Hypofunction, (1) Chronic—Addison's Disease. The description by Addison in 1855 of the symptom complex in association with adrenal lesions, now known by the above name, may be said to form the first fundamental contribution to the pathology of the adrenals, in fact to the study of the endocrine system. The chief features of the affection are pigmentation of the skin and sometimes of the mucous membrane of the mouth, marked asthenia and low blood pressure, emaciation and anæmia in varying degree, and alimentary symptoms such as anorexia, vomiting and diarrhœa. Asthenia is often a well-marked feature, and the muscles become very readily exhausted when any muscular exertion is made. There is also lowering of sexual functions. The nature of the pigmentation has already been described (p. 159) ; it is most marked in parts where pigment is normally abundant and in exposed parts, and it is increased by irritation. For example, in one case observed by us there was an area on the chest darker than elsewhere, which corresponded to the site of application of a mustard poultice.

In addition to these chronic symptoms and signs there also occur in Addison's disease acute exacerbations or crises. In these severe vomiting, fall in blood pressure and extreme asthenia terminating in collapse, occur. We have seen such a crisis in a patient with relatively good health to be precipitated by gross indiscretion in diet. An important fact is that there is increased excretion of sodium chloride and water by the kidneys, resulting in a condition of dehydration with concentration of the blood and rise in the number of red corpuscles per c.mm. There is also increase of blood urea. These facts show that the cortex has an important function in relation to water and salt control.

Nature of Lesions. By far the commonest associated lesion of the adrenals is destruction by chronic tuberculosis ; less common conditions are fibrosis, atrophy, or hypoplasia of the glands. In some instances of the last condition there have been enlargement of the thymus and other endocrine abnormalities. Destruction by tumour growth has sometimes been present, but this is on the whole exceptional. Syphilitic disease has been ascribed as a cause, but we have never found any evidence of this. In quite a number of cases recorded within recent years the cortex of the adrenals has been absent or largely destroyed, while the medulla has been practically unaffected. Such a condition appears to be the result of a toxic necrosis affecting the cortical cells, followed by regeneration and again by necrosis of the hyperplastic parts ; the lesion has been compared to yellow atrophy of the liver. The causation of the condition is unknown but such cases show that loss of cortex is the main factor in the production of the symptoms of Addison's disease.

In a few instances the adrenals have been described as free from morbid change ; but such a statement must be accepted with caution. While the symptoms of Addison's disease usually form a fairly definite picture, this is not always the case and mistaken diagnosis sometimes occurs. It appears that there is no satisfactory evidence that the syndrome of Addison's disease occurs apart from destruction or defect of adrenal tissue.

In the commonest type of tuberculous lesion the adrenals are enlarged, firm, and somewhat irregular on the surface. On section they are seen to be changed into masses of putty-like caseous material, with dense fibrous tissue surrounding it (Fig. 597) ; calcareous deposit is of frequent occurrence. Though the lesion is usually of very long standing, tubercle bacilli may sometimes be found in large numbers. There are also cases where partial destruction by tubercle is associated with some of the symptoms of Addison's disease. Tuberculous lesions are usually present in other organs, e.g., the lungs or lymphatic glands, though in a small proportion of cases the adrenals appear to be affected alone. It is a somewhat striking fact that chronic tuberculosis usually affects both adrenals. In addition to the lesion in the adrenals there is often much fibrous thickening of their capsules and in their neighbourhood, and this may involve the semilunar ganglia and the sympathetic plexus.

Apart from the adrenal lesions the main feature is marked wasting and this involves the muscles as well as the fat. Atrophy of the heart is also noteworthy ; it is often relatively more marked than in other wasting diseases. This is of interest in relation to the low blood pressure. Atrophic change is present also in the testes or ovaries, as the case may be. An interesting fact is that in Addison's disease there is a distinct diminution of the basophile cells of the pituitary (Crooke and Russell).

Pathology. In most cases of Addison's disease we have a picture of a practically complete destruction of a gland essential to life. Compensation for loss of cortex can be effected only by hypertrophy of accessory adrenal tissue, and for loss of medulla by hypertrophy of other chromaffin tissue; for the occurrence of such changes there is no satisfactory evidence. A definite interpretation of symptoms in relation to the structural changes is now, in part at least, possible.

The original view that the tendency to fatigue, low blood pressure, etc., were due to loss of adrenine consequent on destruction of medullary tissue is no longer tenable. This factor is probably not without effect but it is of subsidiary nature. The results of adrenalectomy and their removal by means of cortical extracts, as described above, justify the conclusion that the symptoms are to be ascribed to loss of cortical tissue. The prompt elevation to normal of the blood pressure by such extracts is specially noteworthy. There is also the fact that in some cases of Addison's disease the medullary tissue is intact, while the cortex has been destroyed or is lacking. This view has been fully confirmed by the effects of cortical extracts in cases of the disease. Such extracts containing the active principle or *cortin* have been prepared by Swingle and Pfiffner and by others, and these have made substitution therapy possible to a certain extent. The chronic symptoms have been diminished, and especially the acute symptoms of crises have been relieved. The favourable results in the latter have been enhanced by the specific addition of sodium chloride to the

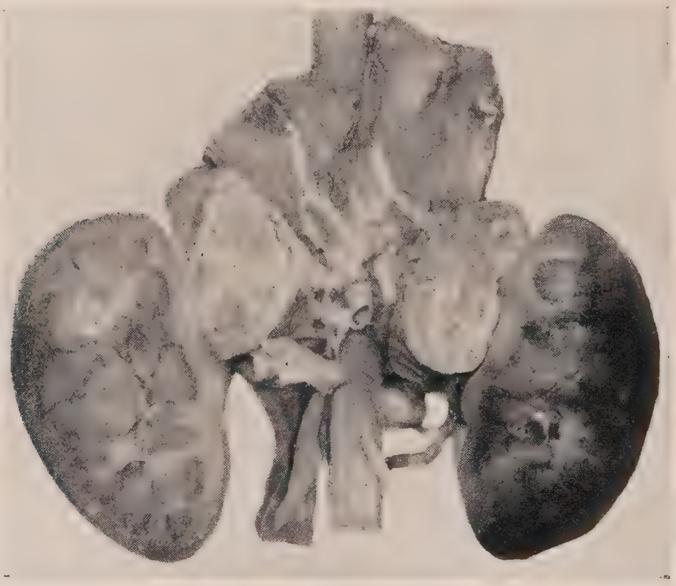

Fig. 597.—Adrenal Glands in a case of Addison's disease, showing caseous destruction and enlargement.

diet. It must be admitted, however, that the proportion of cases in which life has been definitely prolonged is as yet not very large. Dosage has probably been often deficient, as the yield of cortin from adrenal tissue is comparatively small. Of course, such therapeutic measures have no effect on the lesions in the adrenals. Recently Reichstein has prepared from the cortex an active crystalline substance, called by him ‘ corticosterone,’ which promises to give more successful results. This substance has also a stimulating effect on the gonads in both sexes, and may be the means of elucidating more fully the relationship between them and the adrenals.

Indication of deficient supply of adrenalin is given in some cases by the presence of hypoglycæmia and by increased sugar tolerance ; it has further been found that the usual effect of injection of adrenine in causing glycosuria, is diminished.

With regard to the pigmentation, nothing of a definite nature can be stated. It has been shown that a pigment can be formed from adrenalin by the action of an enzyme, and it has been supposed that in Addison’s disease, a substance, possibly tyrosine or an allied body which normally becomes adrenalin, accumulates in the skin and is changed into melanin by oxidation. It is thus likely that the pigmentation is the result of loss of medulla, but this is at present still uncertain. So far as we know the pigmentation has not been observed in adrenalectomised animals.

2. Acute Hypofunction—Adrenal Apoplexy. What may be regarded as a state of acute deficiency occurs sometimes as the result of hæmorrhage into the substance of both adrenals—adrenal apoplexy (Fig. 598). In acute fevers and septic conditions hæmorrhages into the adrenals are occasionally met with and sometimes the hæmorrhage may be so extensive as to cause their complete destruction. The glands are much enlarged and on section their tissue is seen to be occupied by blood clot (Fig. 598). The hæmorrhage is primarily in the medulla, and at the periphery of the glands the cortical tissue is stretched into a thin and irregular layer of yellowish colour and largely necrotic. Such an occurrence is usually attended by symptoms of abdominal pain and marked collapse, and death occurs in a day or two.

In view of the lesions found, it is clear that their effects correspond with those of double adrenalectomy and are to be interpreted accordingly. The destruction of cortical tissue is the essential factor in bringing about the collapse and fatal result. The loss of medullary substance and consequently of adrenine supply can hardly be without some effect, but it is of minor importance. If the hæmorrhage be on one side only, a space or cyst containing altered blood may result. In poisoning with diphtheria toxin, which is associated with marked congestion of the adrenals and minute hæmorrhages, it has been found experimentally that the amount of adrenine is diminished (Ritchie and Bruce). This fact is suggestive as possibly throwing light on the fall of blood pressure which is often present in diphtheria and other infections.

A few facts may here be added with regard to the question of the adrenals and blood pressure. It was shown first by Josué in 1903 that repeated injections of adrenine in rabbits lead to structural changes in the aorta and large vessels. The lesions are mainly of the nature of hyaline change and calcification of the media, and local aneurysmal dilatations may follow. Hypertrophy of the heart also may be produced, and may be accompanied by small areas of necrotic change and fibrosis in the myocardium (Stewart). Some writers have assumed that an increased supply of adrenine plays an important part in leading to arteriosclerosis. The adrenals are often enlarged in arteriosclerosis with hypertonus, but this is due, at least mainly, to cortical enlargement resulting from increased amount of 'myelin' and other fatty bodies in the cells. And, as already stated, a similar accumulation occurs in other conditions when there is an increase of cholesterol in the blood (p. 149). An actual increase of adrenine in the blood in conditions of high blood pressure has not been established. At present there is no evidence that essential hypertension is due to the production of adrenine in excess.

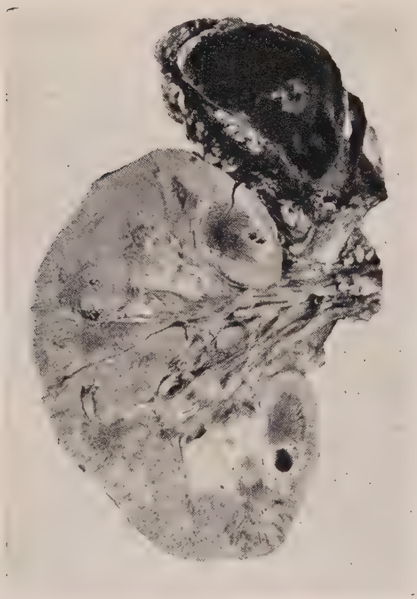

FIG. 598.—Adrenal Apoplexy from a case of sudden death some days after operation. The other adrenal was in a similar condition. × $\frac{3}{5}$.

B. Hyperfunction (1) Cortical—Adrenal Virilism. It may now be regarded as established that the adrenal cortex, in common with the thyroid and anterior lobe of the hypophysis, has an important relation to the sexual functions. Cortical extracts have a stimulating effect on the gonads, whereas cortical absence or deficiency in Addison's disease leads to atrophic changes. Perhaps the most striking fact is that certain tumours of the cortex *in early life* are attended by a precocious development of the sexual organs so that the changes of puberty—development of the external organs of generation, growth of pubic hair, etc.—may occur in a child. Such a condition is known as *pubertas precox*, and the first signs of it have been noted as early as the beginning of the second year of life. In females the secondary sex characters tend to assume the male type, whilst in males there is merely precocious sexual development, attended sometimes by abnormal muscularity. To speak generally, the main effect of such growths is an intensification of maleness and the condition has been spoken of as 'adrenal virilism.' Cases of this kind are much commoner in girls than in boys—in the proportion of five to one (Glynn). Tumours of the same kind occurring *after adolescence* have been attended in the female with an appearance of certain of the characteristics of the male, growth of hair on the chin, coarsening of the skin, alteration of the voice, etc. The tumours in question consist of cortical cells (Fig. 599); they are essentially cortical adenomata, though aberration in type and transition to malignancy occur. Quite a number of such growths have been successfully removed with a dramatic disappearance of the male sex characters as the result. In one or two instances in males there has been a change of the secondary sex characters towards the female type and even the occurrence of lactation has been recorded. The cause of this exceptional occurrence is unknown. Here also a return to normal has followed surgical removal of the growth. Another interesting fact in this connection is that in the state of *pseudo-hermaphroditism* in the female—that is, a condition where the external genitals resemble those of the male, while ovaries are present—enlargement of the adrenals due to cortical hyperplasia has been present in a considerable number of cases. It has been observed that during pregnancy, and in animals during the breeding season, a certain degree of cortical hyperplasia occurs. All these facts go to show the intimate relationship between the adrenal cortex and the sexual functions, and the curious feature is that cortical hyperplasia in the female tends so definitely to call out male characteristics. And it is specially noteworthy that the hyalinisation of the basophile cells of the anterior lobe of the pituitary, which Crooke has shown to be the constant feature of Cushing's syndrome, is present in cases of cortical adenoma of the adrenals, attended by virilism. Recently it has been shown that hypertrophy of the adrenal cortex

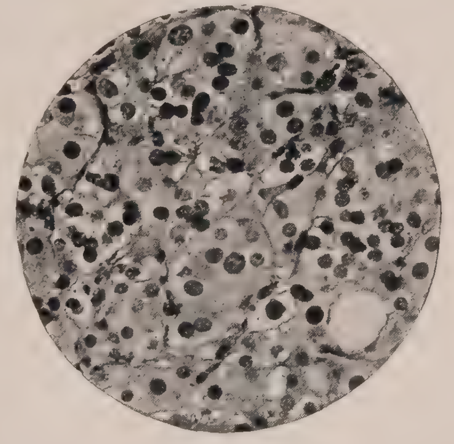

FIG. 599.—Section of cortical Adrenal Adenoma, showing Trabecular Structure with tendency to variation in the types of Cells. Abnormal sexual characters were present. × 250.

with the attendant changes in sexual characters has been found in association with lesions of other endocrine glands, e.g. tumours of the thymus and pituitary.

The effects of removal of cortical adenomata, however, show that they have a direct action in calling forth secondary sex characters, and that the influence is not indirectly transmitted from the pituitary. The close connection between adrenal cortex, gonads and anterior lobe of the pituitary is, however, strikingly illustrated.

Hyperfunction. (2) **Medullary.** The only clear example of this condition is given by chromaffin adenomas or phæocytomas which produce intermittently an increased supply of adrenine, resulting in paroxysmal hypertension. These growths are described below.

Inflammatory and Degenerative Changes. Acute inflammation in the adrenals is of rare occurrence, but evidences of damage in the form of degenerations in the cortical cells, areas of necrosis, etc., are met with in acute infections. These have been observed especially in diphtheria. In fevers and in septic conditions intense congestion and hæmorrhages may be found, and the latter are sometimes of large size (p. 961). Embolic foci are occasionally found in pyæmic states and sometimes small abscesses are produced ; these, however, are rare. It is possible that such acute damage may, as in the case of other organs, be followed by fibrous change, and it has been supposed that fibrotic atrophy leading to Addison's disease may occasionally have such an origin. A toxic necrosis of the cortex followed by absorption and ultimate disappearance would, however, appear to be a more common occurrence (p. 959).

Tuberculous lesions of the more extensive kind are described in connection with Addison's disease. In addition, however, one or two caseous nodules may sometimes be found in the adrenals, in chronic tuberculosis. *Syphilitic lesions* both in the congenital and acquired types present the usual characters ; they are, however, of rare occurrence. In cases of general amyloid disease the adrenals are not infrequently involved ; the amyloid change occurs especially in the capillaries of the cortex and is attended by atrophy of the cortical cells.

Tumours

Certain growths of the adrenals have special features and are of much interest both from the functional and morphological points of view. They may originate either in the cortex or in the medulla.

Of the *cortical* tumours the commonest are *adenomata*. They are fairly common and occur in the form of comparatively small rounded nodules, well defined, and usually of yellow colour, owing to the large amount of myelin and other fat in the cells ; not infrequently they are multiple. Occasionally, an adenoma may reach a large size, and then it may be associated with precocious sexual development as described above. In the smaller adenomata the cells are arranged in trabeculæ and resemble closely those of the zona fasciculata ; but in the larger examples, though the trabecular arrangement is retained for a time, there is a tendency towards alteration in the types of the cells. Vines has recently shown that the cells contain granules which by a certain method of staining are distinctly fuchsinophile ; their significance is not known. The cells may become large, often contain more than one nucleus and all transitions to distinctly aberrant forms are met with. The tumour thus may become a carcinoma, with invasive properties, and formation of secondary growths may follow. Some such malignant growths composed of cells of aberrant type irregularly arranged have been called mixed-cell sarcomata, but by the study of intermediate stages the origin from the cortical cells can be traced. Sometimes both adrenals are the seat of such growths, though one may be involved secondarily.

The tumours originating from the *medulla* are of quite a different order, and three varieties have now been recognised. Two of these take origin from nerve cells, namely the *ganglioneuroma*, a simple growth containing ganglionic nerve cells and nerve fibres, and the *neuroblastoma* or *sympathicoblastoma* composed of embryonic nerve cells or neuroblasts. The characters of these growths have already been described (pp. 224, 255). Neuroblastoma is much the commoner growth, in fact it is fairly frequent in children, and was formerly regarded as a sarcoma, being sometimes described as lymphosarcoma. It may reach a large size, is composed of soft cellular tissue, and is often hæmorrhagic. Secondary growths are often widespread and occur both in other organs and in the bones, those of the skull being not infrequently affected. Similar growths may arise also from other parts of the sympathetic system.

The third variety of medullary tumour takes origin from the chromaffin cells, and to it the term *paraganglioma* or *phæochromocytoma* has been applied. It is composed of polyhedral cells, which usually give the chromophile reaction, staining a brownish-yellow colour with chrome salts, and contain a considerable amount of glycogen. The cells are arranged in solid masses which fill alveolar spaces ; the stroma is somewhat scanty and contains a considerable number of blood vessels. The cells may show somewhat aberrant types, but the growth is usually simple and does not reach a large size. Occasionally cyst-formation has been observed.

A considerable number of cases have now been observed in which a paraganglioma, usually of simple type, has been associated with a definite group of symptoms which appear to have as their basis hyperfunction of the chromaffin tissue with over-production of adrenalin. The symptoms are hypertension which is often of a paroxysmal character, tendency to profuse perspiration and glycosuria, occasionally pulmonary œdema ; the hypertension is associated with arteriosclerosis even in young subjects (Peyron). Occasionally death has occurred from cerebral hæmorrhage. The intermittent character of the hypertension is of interest in view of the supposed 'emergency discharge' of adrenine in normal conditions. Neurofibromatosis has been present in some cases. In a few instances surgical removal of the growth has been followed by disappearance of the symptoms. The occurrence of such functioning growths is of interest as affording a parallel to endocrine tumours elsewhere, e.g. in the islands of Langerhans, pituitary, etc. One or two examples of paraganglioma with similar syndrome have been noted in chromaffin tissues outside the adrenal, e.g. in the organ of Zuckerkandl.

Other tumours may originate from the stroma of the adrenals. Simple growths such as *lipoma, hæmangioma* and *lymphangioma* have been met with, but all of them are rare. *Sarcomata* of various kinds including *melanomata* also occur; not infrequently the growth is bilateral. Secondary growths of *cancer*, less frequently of sarcoma, are occasionally present in the adrenals; here also both glands may be implicated.

Congenital Abnormalities. Absence of both adrenals is sometimes met with, a condition incompatible with life; or one may be absent, and in this condition absence of the right only has been observed (Gierke). An interesting fact is that these abnormalities are intimately related to gross defects of the central nervous system, such as micrencephaly, anencephaly, etc.; in other cases of such cerebral lesions hypoplasia of the adrenals may be present. Apart from such conditions, hypoplasia is of not uncommon occurrence in the condition of status thymico-lymphaticus, and the chromaffin cells have been found to be reduced in number in certain cases; in others, however, the cortex mainly has been affected. It is inferred by some that the hypoplasia implies a deficient supply of adrenine, and that this is an important factor in the liability to sudden death which is noted in the condition. The nature of the hypoplasia, whether primary or secondary, is not known.

Accessory adrenals are of comparatively common occurrence; they are small masses of cortical substance and can be readily recognised by their brownish-yellow colour. They are met with in the surrounding tissues, on the surface or occasionally in the substance of the kidney or liver, and in the region of the ovary or testicle. Occasionally, though rarely, tumour growth arises in connection with them. The relation of these structures to the so-called hypernephromata of the kidney has already been discussed (p. 698).

THE THYMUS

Introductory. Although certain important facts have been established with regard to the thymus as an endocrine gland, much is still unknown both as to its normal functions and the part played by it in conditions of disease. There has been dispute regarding the small round-cells which constitute a large proportion of the active thymus, but the view which has now received most support is that they are really cells of the lymphocyte class, which have invaded the epithelial cells constituting the thymus rudiment. Some observers, however, still hold that they are derivatives of the epithelial cells, and thus essentially different in nature from lymphocytes. In either case, however, one must recognise that an important part of the thymus consists of epithelial cells, namely those of Hassall's corpuscles and those which form the reticular tissue ; and that they are not developmental remains but undergo increase in number after birth and especially in conditions of hyperplasia. The absence in the thymus of germ centres and the lymph paths and sinuses of lymphatic glands, is also a noteworthy point. In view alike of its origin, its structure, and its reactions, the thymus cannot be regarded merely as a mass of lymphoid tissue. Although the weight of the gland in relation to that of the body is greatest at the time of birth, the gland afterwards undergoes a steady increase in size and the maximum actual weight occurs about the fifteenth year. Thereafter involution occurs, and it is to be noted that the beginning of this is related to puberty and not to the complete growth of the body. This fact suggests an intimate relationship between the thymus and the gonads, and experimental results have confirmed such a view. It has been shown that castration of young male animals prevents the usual involution of the thymus. The converse experiment, removal of the thymus, has given contradictory results. Some experimenters have found that hypertrophy of the testes follows, whilst others record atrophic change with increase of the interstitial cells. As will be described below, abnormal enlargement of the thymus or persistence of the thymus is sometimes accompanied by hypoplasia of the genital glands.

The following weights (in grammes) of the thymus at different periods of life, are given by Hammar. The figures within brackets are the weights of the parenchyma alone. At birth, 13·26 (12·33) ; 1–5 years, 22·98 (19·26) ; 6–10 years, 26·10 (22·08) ; 11–15 years, 37·52 (25·18) ; 16–20 years, 25·58 (12·71) ; 21–25 years, 24·73 (4·95) ; 26–35 years, 19·87 (3·87) ; 36–45 years, 16·27 (2·89) ; 46–55 years, 12·85 (1·48).

According to a number of observers, excision of the thymus is followed by diminution in the growth of the bones of the legs, accompanied by thinning and increased porosity, sometimes by a certain amount of softening. Others again have obtained negative results. No definite relationships between the thymus and rickets or other diseases of bone have, however, been established.

Interesting results have recently been obtained by Rowntree and his fellow-workers. They have found that when thymus extract is administered by intraperitoneal injections to rats in successive generations, marked effects are observed in their offspring. There occurs acceleration in the rate of growth and development, whilst the onset of adolescence is hastened ; the young rats breed at an earlier age than the controls and have larger litters. The condition produced is essentially one of precocity ; there is no increase in the ultimate size of the adults. Later results have shown that injection of the females alone is effective in producing precocity. These changes, slight at first, increase in successive generations and ultimately, about the seventh generation, are of a very striking character. There is thus an analogy to what has been described above in connection with the pineal gland, but the effects are much more decided in the case of the thymus.

Status Thymico-lymphaticus. This condition, often spoken of as *status lymphaticus*, has for long occupied a prominent place in the pathological literature of various countries. Till recently it has been generally believed that thymic enlargement in association with general lymphoidal hyperplasia leads to a tendency to sudden death ; and an enlarged thymus is often accepted as a sufficient explanation of the latter. The subject has been critically investigated by a Committee of the Pathological Society of Great Britain and Ireland and of the Medical Research Council, and many of the supposed facts have not stood the application of methods of statistical enquiry. It will be best to give first an account of the condition as it has been generally accepted and then the main findings of the Committee.

In certain individuals, sudden death is apt to occur under such conditions as general anæsthesia, trifling injuries, immersion in cold water, sudden fright, etc. A feeble resisting power to infections has also been noted. These statements hold especially with regard to children, though a similar tendency is met with in adults. In many cases the thymus has been described as being enlarged but there is no doubt that such a statement is often the result of want of knowledge of the normal size of the healthy gland at the particular age. Lymphoid hyperplasia has also been met with. There have been such changes as enlargement of the tonsils and of the follicles at the root of the tongue, of the mesenteric glands and lymphoid tissue of the alimentary tract, etc., the distribution varying in different cases. Lymphoid follicles have also been described in abnormal situations, e.g. in the liver, kidneys and bone-marrow. In addition there have been occasionally found abnormalities in other systems. Among these may be mentioned hypoplasia of the chromaffin system and also, in some cases, hypoplasia of the genital glands along with alterations in the secondary sexual characters. In some cases again hypoplasia of the aorta and its branches has been found. It is to be noted, however, that these abnormalities in the endocrine system and in development are relatively rare and can be concerned in sudden death in only a small proportion of cases. There is no doubt that enlargement of the thymus is met with in the majority of cases of exophthalmic goitre. It occasionally occurs also in acromegaly. The relation of these various changes to one another is undoubtedly an intricate question and can be determined only by properly controlled statistics.

The analysis of the data collected by the Committee has been published by Young and Turnbull, and the following are some of the chief conclusions. The figures obtained show that an abnormally enlarged thymus cannot be considered by itself as indicative of *status thymico-lymphaticus*. There is little, if any, association between the weight of the thymus and the amount of lymphoid tissue in various parts of the body, and no definite evidence of an association between an abnormally large thymus and a general hyperplasia of lymphoid structures. Evidence is also wanting of an association between arterial hypoplasia and an abnormally large thymus. The general conclusion of the Committee is that the facts which have been ascertained afford ' no evidence that the so-called *status thymico-lymphaticus* has any existence as a pathological entity.' This does not imply that there is not a constitutional condition of low resisting power, with tendency to sudden death on slight injuries, etc. ; simply that it is not possible to relate it definitely to thymus and lymphoid hyperplasia. There is a *status*, but it is not justifiable to call it *thymico-lymphaticus*.

Other Changes. Lesions of the thymus in the various other diseases are of rare occurrence. One of the most important points is that the gland is greatly influenced by the state of nutrition, and that in conditions of marasmus and wasting diseases in children it may undergo rapid and marked diminution in size. The cortex undergoes the more marked atrophy, the small round-cells become diminished in number, and at the same time an accumulation of fat and other lipoids occurs in the reticulum. At a later period there is overgrowth of the supporting fibrous tissue, and thus sclerosis may result. It may be mentioned that the thymus, like lymphoid tissue generally, is very sensitive to the action of X-rays ; degenerative changes occur in the lymphocytes, which may become destroyed. We may add also that in early life the thymus has great powers of regeneration, as is seen when a part is removed. Hyperplasia or tumour growth in the thymus has been observed in a considerable proportion of cases of myasthenia gravis (p. 856). Lymphocytic infiltration leading to enlargement of the gland is occasionally met with in lymphatic leukæmia.

In pyæmic conditions suppurative foci may occur in the thymus, and occasionally an abscess may reach a considerable size. In syphilis and tuberculosis the gland is comparatively seldom affected. Small nodules may occur in it in acute general tuberculosis, and occasionally caseous masses are present in association with disease of the neighbouring lymphatic glands, but it is noteworthy that the latter may be extensively involved without lesions being present in the thymus.

Tumours. Malignant growths of the thymus, which are comparatively rare, present a variety of structural features. In some cases they are composed of masses or strands of polyhedral or elongated cells and are clearly carcinomata arising from the cells of the epithelial reticulum ; occasionally there is formation of Hassall's corpuscles. In one or two cases of such growths the syndrome of Cushing's pituitary basophilism has been present and there has been hyalinisation of the basophile cells of the anterior lobe of the pituitary. In others the cells are more isolated and their epithelial characters are less easily recognised ; they are accompanied by an abundant growth of lymphocytes with reticulum formation. Again, the growth may present the features of a lymphosarcoma, being composed of masses of cells resembling lymphocytes, though larger cells with lobate or convoluted nuclei may be intermingled. The real nature of the growth may be doubtful and the term ‘ thymoma ’ is conveniently applied to include malignant tumours of the thymus in general. A thymoma sometimes forms a large mass in front of the heart, and it gives rise to lymphatic infiltration and implication of the lymphatic glands, sometimes also to growths in internal organs. Spindle-cell sarcoma also has been noted.

The occurrence of multiple cysts lined by ciliated epithelium in the thymus has been recorded by different observers. Their origin is doubtful ; it has been ascribed by some to the epithelium of the thymus, by others to dislocated epithelium from the trachea.

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